Original Paper

Effects of AA Amyloidosis on Survival in Peritoneal Dialysis

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Key Words

AA Amyloidosis • Peritoneal dialysis • Mortality

Abstract

Background: To investigate the effects of ESRD etiologies on mortality in peritoneal dialysis patients. **Methods:** We included patients who initiated therapy between 2001-2011 and classified them according to etiologies including amyloidosis, diabetes mellitus, chronic glomerulonephritis and polycystic renal disease. Socio-demographic data, clinical courses and infectious complications were compared between groups, and the reasons for peritoneal dialysis withdrawal were recorded. Patient and technique survival analysis were performed. **Results:** 354 patients were included to the study. Thereafter, 154 patients were excluded. Totally, 29 patients with AA-amyloidosis (mean age 37.9 ± 16.4 years, follow-up time 21.7 ± 20.2 months), 78 patients with diabetes mellitus (mean age 56.9 ± 13.6 years, follow-up time 35 ± 28.6 months), 68 patients with chronic glomerulonephritis (mean age 37.2 ± 12 years, follow-up time 47.7 ± 29.9 months), 29 patients with polycystic renal disease (mean age 35.6 ± 13.8 years, follow-up time 45.4 ± 36.8 months) were evaluated. Albumin level was lower in patients with amyloidosis at initiation and the end of study (for both $p < 0.001$). Incidence of peritonitis and catheter exit site/tunnel infection attacks were higher in patients with amyloidosis ($p = 0.002$ and 0.018 respectively). There was statistical difference among groups with respect to the last status of patients ($p < 0.001$). Deaths were frequent in amyloidotic and diabetic patients. The majority of deaths were due to peritonitis and/or sepsis and, cardiovascular reasons. The mortality rate was found higher in patients with amyloidosis (log rank = 0.005), especially at first 2-3 years. Presence of anyone helping to administer peritoneal dialysis (OR: 6.244 , $p = 0.025$), initial serum albumin level (OR: 0.352 , $p = 0.034$) and presence of catheter exit site/tunnel infection (OR: 0.250 , $p = 0.015$) were independent predictors of patient survival. **Conclusion:** Renal failure etiology has effects on peritoneal dialysis patients' survival. Patients with amyloidosis have the worst survival. Because of loss of PD survival advantage seen in first years of therapy in patients with amyloidosis, peritoneal dialysis may not be suitable as first choice therapy in this group.

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Introduction

Amyloidosis is the term defining a group of diseases characterized by extracellular deposition of proteinic fibrillar material in beta-sheet disposition. The main types of systemic amyloidosis are primary amyloidosis (AL) and secondary amyloidosis (AA) [1]. AA amyloidosis is due to the deposition of serum amyloid A protein in patients which may be complicated by chronic inflammatory diseases, chronic infections, Familial Mediterranean Fever (FMF) and, occasionally malignant diseases [2-7].

Kidneys are often affected by amyloid deposits. Patients typically present with nephrotic syndrome and progressive renal failure, leading to end-stage renal disease (ESRD) [8]. However, data is not adequate regarding patients with systemic amyloidosis undergoing chronic dialysis [5-7, 9, 10]. Role of peritoneal dialysis in treatment of end-stage renal failure complicating systemic amyloidosis has yet to be evaluated. In this study, we aimed to evaluate the effect of ESRD etiology on survival in PD patients.

Materials and Methods

Patients' records undergoing PD in our clinic between 2001-2011 were included to the our retrospective study. Patients who were younger than 18 years, on PD for less than 90 days, having switched to another clinic, whose etiology of ESRD were unknown or the others except amyloidosis, diabetes mellitus, chronic glomerulonephritis, polycystic renal disease, whose renal function recovered and required no longer dialysis were excluded from the study.

The patients were divided into four groups according to ESRD etiologies which were AA-amyloidosis, diabetes mellitus, chronic glomerulonephritis, polycystic renal disease

Age, gender, educational levels of the patients and socio-demographic characteristics such as who helped to administer PD (e.g., themselves, their children or other persons like health caregivers) and the PD preference way (his/her own decision or compulsory choice) were investigated. In our unit, patients have the right to choose the appropriate treatment method after they are informed about renal replacement therapies. However, in the presence of vascular and/or cardiac problems, inavailable hemodialysis center, patients are informed by PD unit staff to direct them towards PD mandatorily. PD preference means choice of PD treatment by patients themselves or by mandatorily because of many causes (vascular problems, cardiac problems, attainability of the center, etc.).

Follow-up time of PD therapy, type of PD modality (CAPD, APD), presence and duration of HD history before PD therapy were investigated. The last status (death, transferred to HD, kidney transplantation or still being followed up) of all patients were recorded.

Systolic and diastolic blood pressure measurements, daily urine volumes, daily mean ultrafiltration amounts, cardiothoracic indices, serum creatinine, calcium, phosphorus, albumin, parathyroid hormone, hemoglobin levels of all patients were recorded at the beginning of the treatment and the during the last visit. Infectious complications including peritonitis, catheter exit site/tunnel infections and their incidences were investigated and all parameters were compared among groups.

Patients' and technique survival analysis were of all patients performed and the effect of AA-amyloidosis on mortality was investigated. Technical failure was defined as transfer to HD due to peritonitis, ultrafiltration failure, inadequate dialysis, exit-site and/or tunnel infection, and mechanical problems.

We performed statistical analyses with the Scientific Package for Social Science (version 13.0; SPSS Inc, Chicago, IL, USA). Kruskal-Wallis and Mann-Whitney U tests were used for nonparametric variables. One-Way ANOVA test was used for analyzing clinical and biochemical parameters among groups. The Kaplan-Meier method was used for measuring patient survival rate. Comparison of outcomes was done by log rank test. We also analyzed the independent risk factors for patient mortality and calculated their hazard ratio (HR) using Cox proportional hazard model backward stepwise LR (Likelihood Ratio) method. Differences were considered statistically significant for p values less than 0.05.

Table 1: Socio-demographic characteristics and parameters of patients

	AA- Amyloidosis (n:29)	Diabetes Mellitus (n:78)	Chronic Glomerulo- nephritis (n:68)	Polycystic Kidney Disease (n:29)	P
Age (years)	37.9±16.4	56.9±13.6	37.2±12	35.6±13.8	<0.001
Gender (Female/Male)	14/15	41/37	44/24	12/17	0.17
Follow up duration (months)	21.7±20.2	35±28.6	47.7±29.9	45.4±36.8	0.003
Hemodialysis history (%)	20.7	21.8	16.2	24.1	0.52
Body mass index (kg/m ²)	21.7±4.5	25±5.1	22.7±3.6	21.1±4	<0.001
Glomerular filtration rate (at the start of PD) (ml/sec/1.73m ²)	9.9±3.2	11±6.2	9.4±3.8	8.7±2.6	<0.001
Cardiothoracic index (%)	44±5.8	49±5	46±6.4	44±6.6	<0.001
Systolic blood pressure (mmHg)	109±20	122±27	119±26	104±27	0.011
Diastolic blood pressure (mmHg)	70±16	76±13	77±15	67±16	0.029
Urine volume (ml/day) (at the initiation of PD)	450±503	401±432	388±441	393±499	0.96
Ultrafiltration amount (at the initiation of PD) (ml/day)	885±550	1030±475	980±400	930±435	0.53
Incidence of peritonitis (months)	14.7±9.2	21.3±21.1	33.4±26.8	31.5±26.6	0.002
Catheter exit site infection attacks (months)	21.7±20.3	29.3±25.7	40.3±28.2	40.3±35.8	0.018

Results

Records of 354 patients with ESRD receiving PD therapy in our PD unit between 2001–2011 were evaluated retrospectively. Totally 150 patients were excluded from the study because of following reasons: 1 patient's renal functions recovered and required dialysis no longer; 4 patient was below 18 years old, 17 patients followed by other PD units and; 8 patients' PD histories were less than 90 days, 120 patients' etiologies of ESRD were unknown or other causes.

Remaining 204 patients' data were evaluated whose 111 were female, mean age at onset of PD was 45±16.6 years and mean duration of PD was 39.9±30.7 months.

Etiology of ESRD was AA amyloidosis in 29 patients 14 of whom were female. Their mean age at onset of PD was 37.9±16.4 years and mean follow-up time was 21.7±20.2 months. Six patients undergone hemodialysis before PD in this group. Etiology of AA amyloidosis was FMF in 18 patients, tuberculosis in 5 patients, bronchiectasia in 4 patients and romatoid arthritis in 2 patients. Diagnosis of amyloidosis was made through renal biopsy in 25 patients and duodenal biopsy in remaining patients.

Diabetes mellitus was the cause of ESRD in 78 patients. Number of patients with chronic glomerulonephritis was 68 and ones with polycystic renal disease was 29. Socio-demographic characteristics of patients according to ESRD etiology are shown in Table 1.

Follow-up duration of AA amyloidosis patients were shorter than the other patients (p=0.003). Diabetic patients were found to be older and had increased body mass index and cardiothoracic index than other groups (p<0.001 for all parameters). Presence of hemodialysis history, daily urine volume and ultrafiltration amounts were found similarly among groups at the initiation of PD (p=0.52, 0.96 and 0.53, respectively).

It was found that 64 % of patients with amyloidosis, 89% of patients with diabetes mellitus, 95% of patients with chronic glomerulonephritis and 96% of patients with polycystic kidney diseases were performing PD treatment by themselves without any help. Rate of patients receiving treatment by the help of their partners, children or caregivers was higher in patients with amyloidosis than the other groups (p<0.001). Nineteen patients (65.5%) with amyloidosis, 62 patients (79.5%) with diabetes mellitus, 62 patients (91.2%) with chronic glomerulonephritis and 24 patients (82.7%) with polycystic kidney disease started peritoneal dialysis by own decision. Rate of compulsory choice of PD was statistically higher in patients with amyloidosis than the other groups (p<0.001).

Table 2: Biochemical analysis and whole blood count of patients

	Amyloidosis (n:29)	Diabetes Mellitus (n:78)	Chronic Glomerulo- nephritis (n:68)	Polycystic Kidney Disease (n:29)	P
Kt/V urea	1.74±0.3	2.02±0.58	2.2±0.48	2.19±0.4	0.014
Creatinine clearance	48±14	60±23	61±17	67±22	0.07
D/Pcr 4 th hours	33.3/8.3/	16.7/37/	15.3/40.7/	13.6/40.9/	0.63
(H/HA/LA/L)* (%)	50/8.4	37/9.3	30.5/13.5	31.9/13.6	
Initial albumin level	2.7±0.8	3.4±0.5	3.7±0.6	3.8±0.4	<0.001
Initial PTH level	192±146	270±218	339±338	465±497	0.018
Initial calcium level	8.6±1.3	8.8±0.8	9±1.1	9±1.0	0.27
Initial hemoglobin level	10.6±2	10.6±1.7	10.2±1.6	10.6±2.2	0.62
Last albumin level	3.04±0.6	3.48±0.4	3.8±0.5	3.96±0.5	<0.001
Last PTH level	284±276	294±250	548±614	479±405	0.006
Last calcium level	8.6±1.2	9.1±1.0	9.3±0.8	9.3±1.0	0.056
Last hemoglobin level	10.9±1.8	11.6±2.0	11±1.9	11.8±1.8	0.11

(H/HA/LA/L)*= High/High average/Low average/Low

Table 3: Last status and causes of death according to groups

		Amyloidosis (n:29)	Diabetes Mellitus (n:78)	Chronic Glomerulo- nephritis (n:68)	Polycystic Kidney Disease (n:29)
Causes of death	Peritonitis/sepsis (%)	6(42.8)	10(41.7)	6(50)	1(25)
	Cardiovascular (%)	3(21.4)	11(45.8)	3(25)	2(50)
	Malnutrition (%)	2(14.4)	1(4.2)	2(16.7)	-
	Unknown (%)	3(21.4)	2(8.3)	1(8.3)	-
	Inadequate dialysis	-	-	-	1(25)
	Total death (n)	14(48.3%)	24(30.7%)	12(17.6%)	4(13.8%)
Transferred to hemodialysis (%)		6(20.7)	22(28.2)	14(20.6)	6(20.7)
Transplantation		3(10.3)	14(18%)	20(29.4)	7(24.1)
Follow-up		6(20.7)	18(23.1)	22(32.4)	12(41.4)

Biochemical analysis and whole blood count data are shown in Table 2. Serum albumin level was significantly lower in patients with amyloidosis at the initiation and the last visit ($p<0.001$ for both). Initial Kt/V, initial and last parathormone levels were also significantly lower in patients with amyloidosis ($p=0.014$, 0.018 and 0.006 , respectively).

Incidence of peritonitis ($p=0.002$) and catheter exit site/tunnel infection ($p=0.018$) were statistically higher in patients with amyloidosis when compared with other etiologies (Table 1).

The last status and causes of death are shown in Table 3. Death rate (48.3%) was higher in patients with AA amyloidosis while transplantation (10.3 %) and follow-up (20.7 %) rate was lower according to other groups. Statistically significant difference among groups with respect to the last status of patients was present ($p<0.001$). The most common causes of death were cardiovascular reasons, peritonitis and/or sepsis for all groups. There was no significant difference among four groups in terms causes of death ($p=0.41$).

With Kaplan-Meier analysis, median patient survival time was 31(6.7-55.3) months in amyloidotic patients. It was 44 (28.2-59.8) months in patients with diabetes mellitus, 79 (52.7-105.3) months in patients with chronic glomerulonephritis and 63 (16-109) months in patients with polycystic kidney disease. The mortality rate was evaluated at 1, 3, and 5 years and it was found higher in amyloidotic patients (log rank=0.005) (Fig. 1- Table 4).

Fig. 1. Survival rates of all groups.

Fig. 2. Technique survival of all groups.

Age, initial Kt/V, initial creatinine clearance (CrCL), 4th hour D/Pcreatinine, body mass index (BMI), initial serum hemoglobin iPTH, calcium, phosphate, albumin levels, PD preference, who helped administer the PD, presence of peritonitis and catheter exit site/tunnel infection were analyzed using Cox proportional hazard model backward stepwise LR(Likelihood Ratio) to identify independent risk factors of mortality. Presence of anyone to administer PD (OR: 6.244, 95% CI: 1.261-30.916, $p=0,025$), initial serum albumin level (OR: 0.352, 95% CI: 0.134-0.927, $p=0,034$) and presence of catheter exit site/tunnel infection (OR: 0.250, 95% CI: 0.082-0.764, $p=0,015$) were found to be independent predictors of patient survival.

Table 4: Patient and technique survival rates of all patients

		Amyloidosis (n:29)	Diabetes Mellitus (n:78)	Chronic Glomerulo- nephritis (n:68)	Polycystic Kidney Disease (n:29)
Patient survival	1 st year (%)	68.4	80.1	100	93.8
	3 rd year(%)	39.1	56.4	82.2	82
	5 th year(%)	19.5	35.7	63.3	41
Technique survival	1 st year (%)	78.6	97.1	92.2	83
	3 rd year(%)	56.1	83.2	62.6	52
	5 th year(%)	37.4	44.6	43.4	52

With Kaplan–Meier analysis, median technique survival time was 46.5 ± 6.7 months in amyloidotic patients. It was 67.3 ± 5.8 months in patients with diabetes mellitus, 60 ± 6.9 months in patients with chronic glomerulonephritis and 49.2 ± 12.8 months in patients with polycystic kidney disease. The technique survival rates at 1, 3 and 5 years by Kaplan–Meier analyses were shown in Table 4. The technique survival rates were found similar among groups (log rank=0.238) (Fig. 2).

Age, initial Kt/V, BMI, PD preference, who helped administer the PD, initial CrCL, serum albumin and hemoglobin levels, presence of peritonitis and catheter exit site/tunnel infection were analyzed using Cox proportional hazard model backward stepwise LR(Likelihood Ratio) to identify independent risk factors of technique survival. Only presence of catheter exit site/tunnel infection (OR: 0.288, 95% CI: 0.106-0.785, $p=0.015$) was found to be predictor of technique survival.

Discussion

There was significantly difference between patients with AA amyloidosis and other groups in terms of Kt/Vurea, initial and last serum albumin levels, incidence of peritonitis and catheter exit site infections and survival in our study.

Systemic amyloidosis presents with a variety of signs and symptoms. The kidney is the most frequently affected one (80-90%), conferring a poor prognosis and high morbidity along the progression of the disease [9-11]. Although the outcomes of dialysis among patients with end-stage renal disease caused by AA amyloidosis have generally been found to be comparable to those of patients with other causes of ESRD, in many of these studies, they indicate that survival in AA amyloidosis is worse according to all other causes. Negative effects on survival in AA amyloidosis more HD patients reported [3-7, 9, 10, 12]. However, there are only a few data on PD patients [11, 13].

Martinez-Vea, et al. [14] compared 48 HD patients with systemic amyloidosis with 63 nondiabetic HD patients without amyloidosis. Amyloidotic patients had higher morbidity and mortality rates. Altiparmak, et al. [13] reported that there was no significant difference between the FMF induced amyloidosis and other causes of ESRD in terms of efficiency of CAPD, peritoneal function, complications and, survival. The patients with diabetic nephropathy had shorter survival period compared to patients with chronic glomerulonephritis and chronic interstitial nephritis, but there was no survival difference between FMF-amyloidosis patients and other groups. It's mentioned in the short term survival in this study [13].

Martinez Vea, et al. [14] showed survival rate of 72%, 62%, and 44% at one, two, and six years by analysis of 48 patients on dialysis with systemic amyloidosis. Moroni, et al. [3] investigated 43 Italian patients on dialysis with amyloidosis. One-year and five-year survival rate was 68% and 30%, respectively, with no difference shown by type of dialysis chosen. Esteve, et al. [15] observed that survival at 6, 12, and 24 months was 62%, 55% and 44% for AA amyloidosis, respectively. The results from our series were slightly lower. We found that AA amyloidosis is a poor prognostic factor for survival in PD patients.

Prognosis for patients with AA amyloidosis is difficult to determine from published series. However, the mean survival time after the onset of renal replacement therapy was reported as 2.11-3.05 years in rheumatology units [16]. Mean survival time was reported as between 8.5-32 months in nephrology units for patients with AA amyloidosis [5, 6, 17-19]. However, the majority of the data about AA amyloidosis was reported in hemodialysis patients. Most of the patients died as a result of progression of extrarenal disease, in particularly, infection, or as a result of malnutrition. In our study, median survival time was found 31 months for PD patients with AA amyloidosis. It was shorter than the other groups.

In previous studies, investigators were reported that PD was advantageous in terms of survival compared to HD in the first 2-3 years of treatment and afterwards and survival with PD was equal or worse than HD [20, 21]. Many studies showed that survival rate of patients with secondary amyloidosis undergoing HD was 60-82% at 1 year, 37% at 3 years, 18-46% at 5-6 years [2, 7, 9, 12, 16]. The results of survival rates from our series were similar to other published studies. Survival advantage of PD at first years of treatment was lost in patients with amyloidosis.

Initial serum albumin level was found to affect mortality significantly in many studies [22-24]. PD may be contraindicated in patients with malnutrition and low serum albumin level. Sahin S et al. [11] reported serum albumin levels of patients with FMF amyloidosis undergoing PD treatment were lower than the patients with ESRD secondary to other diseases. In our study, we detected low serum albumin levels in AA amyloidosis group and it was shown to be a predictive factor on mortality.

Infectious complications cause significant morbidity and mortality in PD patients [25, 26]. Sahin S et al. [11] reported that frequency of infections in patients with FMF amyloidosis was higher (4.2 vs 0.5) than the patients with ESRD secondary to other diseases in CAPD group. Another study [13] found no difference between the FMF-amyloidosis group and other groups in terms of efficiency of CAPD, peritoneal function and, complications. In our study, frequency of peritonitis and catheter exit site infections were found higher in patients with AA amyloidosis than the patients with ESRD secondary to other diseases. Besides this, we found that the only factor affecting AA amyloidotic patient's survival significantly was the presence of catheter exit site/tunnel infection.

Patients with chronic kidney diseases (CKD) should be timely incorporated into educational programmes to allow optimal choice of a dialysis method based on patient preference as well as medical indications and contraindications [27]. Peritoneal dialysis requires a significant patient compliance, family support and a clear understanding about the application technique. PD as the first choice of treatment modality, applicated treatment under suitable conditions and own wishes is reported to be altering the survival rates favourably [28]. In our study, we found that administration of PD by anyone other than the patient may affect the survival.

The main limitation of the present study is its retrospective design. Analysis of other factors that have also been associated with mortality, such as inflammation, renal clearance. The measurement of residual renal function was assessed by daily urine volume. Renal clearance and urine protein excretion amount were not calculated. Planned and unplanned patients were not compared in this study the effect of this parameter on mortality could not be calculated.

Conclusion

Etiology of ESRD, has effects on patient survival in PD patients. Among all etiologies, AA amyloidosis has the worst survival rate. PD survival advantage seen in first years of therapy was not seen in patients with amyloidosis. PD may not be suitable renal replacement therapy choice in patients with end-stage renal disease (ESRD) due to AA amyloidosis. Therefore, in patients with amyloidosis, if serum albumin level was low and PD therapy would be performed by another person, HD should be the first choice.

Conflict of Interests

There aren't any non-financial competing interests we would like to declare in relation to this paper. We haven't any other financial competing interests.

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