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# Long-Term Survival of Peritoneal Dialysis in Children: A Cohort Study

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***Abstract***

***Background:*** There is little information about the survival rate of pediatric peritoneal dialysis (PD) patients and its risk factors. Therefore, the aim of the present study was to assess survival rate and its risk factors in Iranian children undergoing PD.

***Materials and Methods:*** Demographic and laboratory data of 407 Iranian children (up to 19 years old) undergoing PD, from 20 centers in Iran were included. The outcome of interest in our study was survival rate and determination of its risk factors in PD children. The joint models of longitudinal and time-to-event data analysis was used.

***Results:*** The median duration of follow-up was 537 (interquartile range: 146 to 1,177) days. Finally, 72 (17.7%) patients died during a period of 23 years. Our results showed that one-year survival rate of PD patients was 93.6% and five-year survival rate was 76.9%. In addition, the most important risk factors for the PD all-cause mortality were age (HR=0.9301; 95% CI: 0.9031 to 0.9587), serum creatinine (HR=0.8907; 95% CI: 0.8138 to 0.9750), platelet count (HR=0.9999; 95% CI: 0.99995 to 0.99999), aspartate aminotransferase level (HR=1.0001; 95% CI: 0.9999, 1.0002), alkaline phosphatase (HR=0.9989; 95% CI: 0.9982 to 0.9997), renal solute clearance rate (HR=0.9839; 95% CI: 0.9700 to 0.9981), and normalized protein catabolic rate (HR=0.4031; 95% CI: 0.1879, 0.8648).

***Conclusion:*** The survival rate of Iranian pediatric PD patients is similar to other countries. It is suggested that laboratory assessment be continually evaluated in PD patients to reduce the risk of death.

***Key Words:*** Children, Mortality, Peritoneal Dialysis, Survival; Risk Factors.

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## 1- INTRODUCTION

Peritoneal dialysis (PD) is an effective therapy in the children with end-stage renal disease (ESRD) awaiting transplantation (1). Peritoneal dialysis is one of the most attractive and economical therapeutic methods for management of chronic kidney injury (2). Regarding the direction of most scientific studies to reduce the cost and burden of disease, instead of kidney transplantation, today, dialysis is used to treat renal failure (3). PD is the second alternative therapy after hemodialysis. PD is the most common type of outpatient. Today, 12% of patients with chronic renal failure in the United States are treated with this method. In Asian developing countries, 15% of patients are treated with PD and very successful reports are published in this group of countries (2).

Survival and quality of life reported from patients undergoing PD are similar to those who use hemodialysis (4). The inherent domestic use and flexibility of PD is its advantage tohemodialysis (5). Overall survival of patients in the first year of PD is 86.8% and 10-year survival is about 11.3% (6). Unfortunately, several reports have shown that PD treatment is not more favorable than hemodialysis after the first two years of treatment (7). Therefore, the study of risk factors of mortality in PD patients is one of the most important challenges (8). Many factors could play a role in PD survival, including age, high level of ferritin, serum albumin, nutritional status, recurrent peritonitis, the hemodialysis transition of increasing numbers of patients who have undergone transplantation, PD catheter-related technical problems and the patient's socio-economic status (9, 10). However, there is little information about the survival rate of pediatric PD patients and its effective factors in the world, and so far no similar study has been conducted in Iran on children. Therefore, the aim of the present study was to assess survival rate and all-cause mortality risk factors of PD in Iranian children and adolescents.

## 2- MATERIALS AND METHODS

### 2-1. Study design and setting

In this cohort study demographic and laboratory data of 407 (up to 19 years old) Iranian patients undergoing peritoneal dialysis (PD), from 20 Continuous ambulatory peritoneal dialysis (CAPD) centers in Iran were used. These data were extracted from the Iranian PD registry that were entered using Hakim software (Electronic Health Record: Pegahsoft, Tehran, Iran). The PD registry included data on patients from 1995 up to February 2018. Ethic Committee of Tehran University of Medical Sciences approved the protocol of present study.

### 2-2. Participants

Patents aged under 20 years old were included. Patients with incorrect data input were excluded. Eleven patients were removed due to incorrect follow-up time input or unknown event condition.

### 2-3. Measurements

In the Iranian PD registry, data on peritoneal dialysis patients were collected in 20 centers. Patients visited the perinatal dialysis registry centers every six months, and trained nurses reviewed their anthropometric and laboratory data. The variables included demographic and anthropometric data, hematological parameters, serum levels of anions and cations, blood glucose levels and lipid profile, blood urea nitrogen and creatinine levels, liver enzymes and renal function indices.

### 2-4. Outcome

The outcome of interest in our study is survival and determination of its risk factors in PD children.

### 2-5. Statistical analysis

After describing baseline characteristics of the patients under study and providing summary information on their laboratory measures, univariate Cox regression was employed for preliminary identification of the potential risk factors of survival. Afterwards, a backward variable selection procedure in multivariate Cox regression (with p-value < 0.1), was used to identify the potential baseline risk factors of survival in peritoneal dialysis patients after adjusting for the possible confounders using the R programming language.

R statistical software was subsequently used to analyze the data using joint modeling of longitudinal and time-to-event data. The joint model includes two sub models, in the case of our study the PD patients follow up (longitudinal process), and the risk factors of survival of PD patients (event process). It is worth mentioning that in studies whereby the percentage of event (risk factors of survival) is small (at most 20 to 30%), the Cox regression is not the best model for analyzing the data. Several literatures recommend the use of cure or joint models. For the type of joint model used in our analysis, it is customary to model the effect of the potential important baseline risk factors of the event (usually found by Cox regression) simultaneously on an important predictor of the event like BUN (Blood Urea Nitrogen) in our study (as a biomarker), and the event (risk factors of survival in peritoneal dialysis patients).

Usually, using a backward variable selection procedure to finally find the best set of independent baseline risk factors of survival is required. In order to obtain robust result in joint modeling procedure, we standardized our variables before entering them into the model (11). This finding was validated by comparing the AIC and BIC of different methods of fitting the sub models. In our study, mortality rate was observed in 17.69% of the patients, the joint modeling of patients' follow-up data (with BUN as a biomarker), and the time of risk factors of survival of PD patients were used to model the data, and were found to be the most accurate. The joint models of longitudinal and time-to-event data are made of two parts: longitudinal sub model and survival sub model. Longitudinal sub model was fitted with mixed effect models in 3 common ways: random intercept, random intercept plus random slope and flexible splines. Afterwards, the AIC (Akaike Information Criterion), and BIC (Bayesian Information Criterion) were used to find out the best longitudinal and event sub models among the other candidates. P-value <0.05 was used to determine statistical significance in the final joint model. The variables under study were standardized to avoid the effect of different units of measurements which produce robust results.

## 3- RESULTS

Data of 407 PD patients were analyzed (Mean age: 9.0±6.4 years old; 50.8% boys). The median duration of follow-up was 537 (interquartile range: 146 to 1177) days. Finally, 72 (17.7%) patients died during the 23 years. The demographic and laboratory tests are presented in **Table.1**. Kaplan Meier survival curve of PD patients is presented in **Figure.1**. One-year survival rate of PD patients was 93.6% and five-year survival rate was 76.9%. Results of univariate and multivariate cox regression are presented in **Table.2**. The multivariate cox regression showed that age at beginning of PD (Hazard ratios [HR]=0.934; 95% confidence interval [CI]: 0.907 to 0.963), appetite status (HR=0.498; 95% CI: 0.252 to 0.983), serum creatinine level (HR=0.900; 95% CI: 0.828 to 0.927), serum sodium level (HR=0.969; 95% CI: 0.935 to 1.003), aspartate aminotransferase level (HR=1.005; 95% CI: 1.001 to 1.009), alanine aminotransferase level (HR=0.999; 95% CI: 0.998 to 1.001), renal solute clearance rate (HR=0.987; 95% CI: 0.975

to 0.999) and normalized protein catabolic rate (HR=0.350; 95% CI: 0.161 to 0.767) are potential predictor factors of PD patients survival. Joint model analysis showed that when all measured variables are held constant, 1 year lower baseline age will result in 7.5% larger risk of all-cause mortality (HR=0.9301; 95% CI: 0.9031 to 0.9587). In addition, 1 mg/dl lower level of baseline creatinine is associated with a 12.27% larger risk of all-cause mortality (HR=0.8907; 95% CI: 0.8138 to 0.9750). Moreover, 1 unit lower level of baseline platelet (HR=0.9999; 95% CI: 0.99995 to 0.99999), 1 IU/l lower level of baseline alkaline phosphatase protein (HR=0.9989; 95% CI: 0.9982 to 0.9997), 1 unit lower level of baseline renal solute clearance rate (HR=0.9839; 95% CI: 0.9700 to 0.9981), 1 unit lower normalized protein catabolic rate (HR=0.4031; 95% CI: 0.1879, 0.8648) and 1 IU/l greater level of aspartate aminotransferase (HR=1.0001; 95% CI: 0.9999, 1.0002) is associated with 0.0003%, 0.11%, 1.63%, 148% and 0.01% increase in the relative risk of all-cause mortality (**Table.3**).

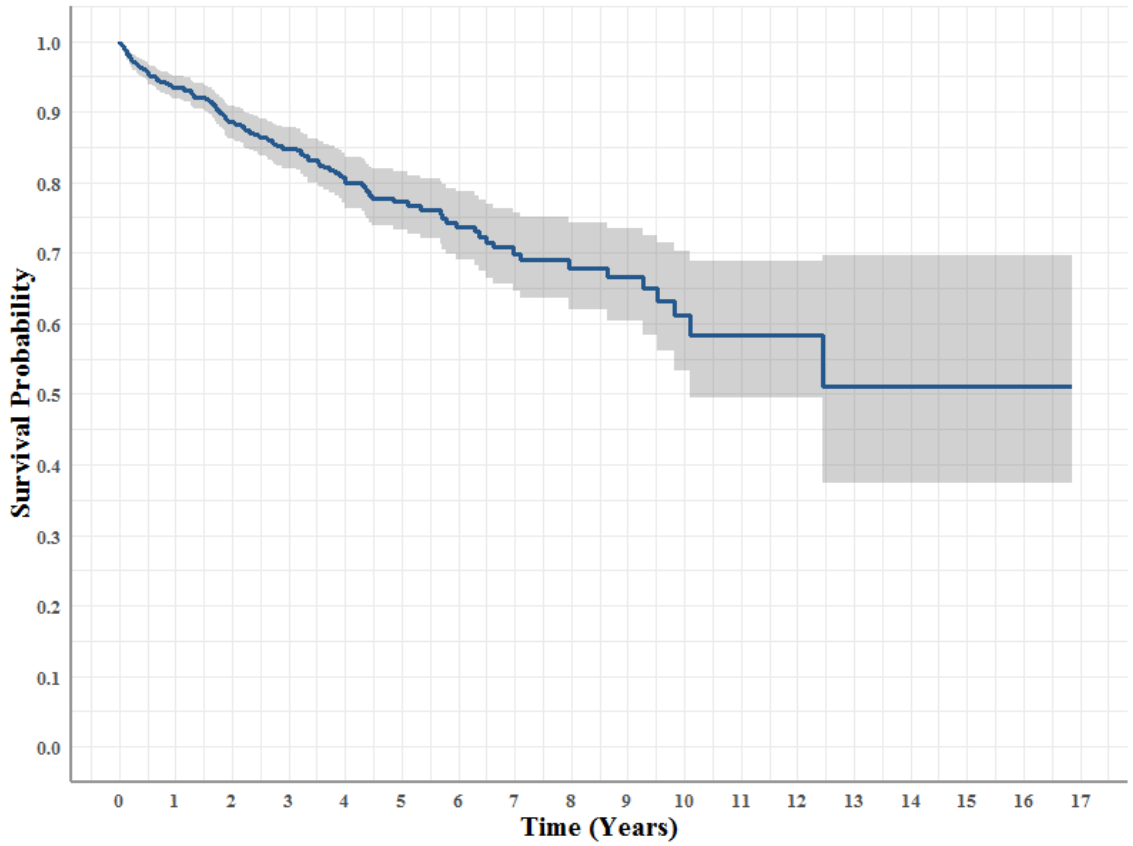


**Fig.1**: Kaplan Meier survival analysis curve of peritoneal dialysis patients.

**Table-1**: Baseline demographic and laboratory characteristics of the studied patients before starting peritoneal dialysis.

| Variables | Alive (n=335) | Died (n=72) |
|---|---|---|
| Age | 9.7±6.2 | 5.4±5.8 |
| Sex (%) | | |
| Boys | 166 (49.6) | 35 (48.6) |
| Girls | 169 (50.45) | 37 (51.4) |
| Weight (kg) | 44.7±20.0 | 49.4±17.0 |
| Height (cm) | 130.1±30.8 | 124.2±34.3 |
| Appetite (%) | | |
| High | 23 (6.9) | 1 (1.4) |
| Medium | 279 (83.3) | 65 (90.3) |
| Low | 33 (9.8) | 6 (8.3) |
| Systolic blood pressure (mmHg) | 122.3±20.5 | 124.5±18.5 |
| Diastolic blood pressure (mmHg) | 75.3±12.1 | 76.5±11.8 |
| White blood cell count (count) | 7491.2±2533.3 | 7990.7±1992.0 |
| Hemoglobin (g/dl) | 9.7±1.9 | 10.2±1.8 |
| Platelet count (count) | 251704.6±88469.1 | 241574.3±53616.1 |
| Erythrocyte sedimentation rate (mm/hr) | 56.6±22.1 | 61.1±17.6 |
| Creatinine (mg/dl) | 6.4±2.2 | 6.3±2.2 |
| Sodium (mEq/l) | 137.9±5.3 | 136.9±5.5 |
| Potassium (mEq/l) | 4.6±0.8 | 4.6±0.6 |
| Phosphate (mg/dl) | 5.4±1.5 | 5.3±1.5 |
| Fasting blood sugar (mg/dl) | 109.6±38.0 | 123±37.5 |
| Blood urea nitrogen (mg/l) | 72.5±34.2 | 72.8±33.7 |
| Calcium (mg/dl) | 8.8±0.9 | 8.8±1.0 |
| Total cholesterol (mg /ml) | 192.5±40.9 | 197.3±47.6 |
| HDL cholesterol (mg/dl) | 42.2±7.2 | 42.4±6.0 |
| LDL cholesterol (mg/dl) | 109.2±28.6 | 111.7±32.2 |
| Triglyceride (mg/dl) | 193.2±100.3 | 192.4±78.8 |
| Alkaline phosphatase protein (u/l) | 451.2±329.4 | 380.4±186.4 |
| Iron (g/l) | 81.6±29.5 | 81.6±46.4 |
| Transferrin, total iron-binding capacity (mcg/dl) | 286.6±70.3 | 294.9±98.1 |
| Ferritin (ng/ml) | 358.6±260.0 | 384.6±219.0 |
| Aspartate aminotransferase (u/l) | 26.6±10.0 | 34.3±69.1 |
| Alanine aminotransferase (u/l) | 28.1±64.4 | 26.8±1.6 |
| Parathyroid hormone (pg/ml) | 265.4±165.6 | 225.0±147.5 |
| Albumin (g/dl) | 3.8±0.4 | 3.7±0.5 |
| Urine volume rate (ml/day) | 613.9±414.7 | 530.4±321.2 |
| Ultrafiltration rate (ml/day) | 856.2±371.0 | 929.4±386.6 |
| Renal solute clearance rate (%) | 25.8±18.0 | 24.5±14.8 |
| Peritoneal solute clearance rate (%) | 47.0±8.0 | 48.0±6.4 |
| Total solute clearance rate (%) | 73.9±20.8 | 74.1±21.5 |
| Glomerular filtration rate (ml/min) | 2.5±2.1 | 2.5±1.8 |
| Renal Kt/V | 0.5±0.3 | 0.5±0.3 |
| Peritoneal Kt/V | 1.6±0.3 | 1.7±0.3 |
| Total Kt/V | 2.1±0.4 | 2.1±0.3 |
| Normalized protein catabolic rate (g/kg/day) | 1.1±0.2 | 1.0±0.2 |

**Table-2**: The results of Cox regression of the risk factors of all-cause mortality.

| Demographic characteristics | Univariate | | Multivariate | |
|---|---|---|---|---|
| | HR (95% CI) | P-value | HR (95% CI) | P-value |
| Age | 0.942 (0.916, 0.968) | <0.0001 | 0.934 (0.907, 0.963) | <0.0001 |
| Sex | 0.799 (0.574, 1.115) | 0.187 | 1.275 (0.899, 1.809) | 0.173 |
| Weight | 1.007 (0.999, 1.016) | 0.089 | --- | --- |
| Height | 0.995 (0.989, 1.002) | 0.188 | --- | --- |
| Appetite | | | | |
| High | *Reference* | --- | *Reference* | --- |
| Medium | 1.191 (0.470, 3.018) | 0.713 | --- | --- |
| Low | 1.775 (0.931, 3.384) | 0.082 | 0.498 (0.252, 0.983) | 0.044 |
| Systolic blood pressure | 1.006 (0.997, 1.015) | 0.198 | --- | --- |
| Diastolic blood pressure | 1.006 (0.991, 1.021) | 0.423 | --- | --- |
| White blood cell count | 1.000 (1.000, 1.001) | 0.113 | --- | --- |
| Hemoglobin | 1.037 (0.955, 1.126) | 0.388 | --- | --- |
| Platelet count | 1.000 (1.000, 1.001) | 0.213 | 0.999 (0.998, 0.9) | 0.004 |
| Erythrocyte sedimentation rate | 1.002 (0.994, 1.009) | 0.628 | --- | --- |
| Creatinine | 0.980 (0.920, 1.044) | 0.537 | 0.900 (0.828, 0.927) | 0.013 |
| Sodium | 0.971 (0.938, 1.004) | 0.088 | 0.969 (0.935, 1.003) | 0.077 |
| Potassium | 1.078 (0.876, 1.326) | 0.481 | --- | --- |
| Phosphate | 1.001 (0.888, 1.130) | 0.982 | --- | --- |
| Fasting blood sugar | 1.004 (1.001, 1.007) | 0.022 | --- | --- |
| Blood urea nitrogen | 1.000 (0.995, 1.004) | 0.873 | 1.004 (0.999, 1.010) | 0.135 |
| Calcium | 1.018 (0.853, 1.214) | 0.845 | --- | --- |
| Total cholesterol | 1.001 (0.997, 1.005) | 0.622 | --- | --- |
| HDL cholesterol | 1.002 (0.980, 1.025) | 0.832 | --- | --- |
| LDL cholesterol | 1.002 (0.997, 1.008) | 0.445 | --- | --- |
| Triglyceride | 1.000 (0.998, 1.002) | 0.969 | --- | --- |
| Alkaline phosphatase protein | 0.999 (0.999, 1.000) | 0.019 | --- | --- |
| Iron | 0.999 (0.994, 1.004) | 0.731 | --- | --- |
| Transferrin, total iron-binding capacity | 1.001 (0.999, 1.003) | 0.319 | --- | --- |
| Ferritin | 1.000 (1.000, 1.001) | 0.208 | --- | --- |
| Aspartate aminotransferase | 1.003 (0.999, 1.007) | 0.109 | 1.005 (1.001, 1.009) | 0.008 |
| Alanine aminotransferase | 1.000 (0.994, 1.006) | 0.919 | 0.999 (0.998, 1.001) | 0.096 |
| Parathyroid hormone | 0.998 (0.997, 0.999) | 0.008 | 0.999 (0.998, 1.001) | 0.100 |
| Albumin | 0.586 (0.396, 0.867) | 0.007 | --- | --- |
| Urine volume rate | 1.000 (1.000, 1.001) | 0.655 | --- | --- |
| Ultrafiltration rate | 1.000 (1.000, 1.001) | 0.515 | --- | --- |
| Renal solute clearance rate | 0.998 (0.989, 1.008) | 0.735 | 0.987 (0.975, 0.999) | 0.034 |
| Peritoneal solute clearance rate | 1.001 (0.979, 1.023) | 0.943 | --- | --- |
| Total solute clearance rate | 1.001 (0.992, 1.009) | 0.893 | --- | --- |
| Glomerular filtration rate | 1.014 (0.935, 1.100) | 0.731 | --- | --- |
| Renal Kt/V | 0.857 (0.498, 1.475) | 0.577 | --- | --- |
| Peritoneal Kt/V | 1.169 (0.663, 2.060) | 0.590 | --- | --- |
| Total Kt/V | 0.883 (0.569, 1.370) | 0.579 | --- | --- |
| Normalized protein catabolic rate | 0.441 (0.220, 0.882) | 0.021 | 0.351 (0.161, 0.767) | 0.009 |

HR: hazard ratio; 95% CI: 95% confidence interval.

**Table-3**: Independent risk factors of all-cause mortality.

| Risk factors | β (±SE) | HR | 95% CI | P-value |
|---|---|---|---|---|
| Age | -0.0725 (±0.0150) | 0.9301 | 0.9031, 0.9587 | <0.0001 |
| Creatinine | -0.1157 (±0.0461) | 0.8907 | 0.8138, 0.9750 | 0.012 |
| Platelet | -0.000003 (±0.000001) | 0.9999 | 0.99995, 0.99999 | 0.0056 |
| Alkaline phosphatase protein | -0.0011 (±0.0004) | 0.9989 | 0.9982, 0.9997 | 0.0101 |
| Renal solute clearance rate | -0.0162 (±0.0073) | 0.9839 | 0.9700, 0.9981 | 0.026 |
| Normalized protein catabolic rate | -0.9085 (±0.3894) | 0.4031 | 0.1879, 0.8648 | 0.0198 |
| Aspartate aminotransferase | 0.0001 (±0.00007) | 1.0001 | 0.9999, 1.0002 | 0.0408 |

HR: hazard ratio; 95% CI: 95% confidence interval; SE: Standard error.

## 4- DISCUSSION

Peritoneal dialysis is one of the most common alternative renal methods for patients with end stage renal disease, which is used to maintain the remaining kidney function and reduce cardiovascular instability (12). This method is less costly than hemodialysis, with comparable survival rates and better quality of life than hemodialysis (13). Our results showed that one-year survival rate of PD patients was 93.6% and five-year survival rate was 76.9%. These results are consistent with the findings of earlier studies. In all studies in the United States, Europe, Japan and Turkey, the survival rate for children is more than 90% and a five-year survival of over 80% (14). In this study, the risk factors of PD patient mortality was evaluated. According to our findings after adjusting for confounding factors, the most important reasons for the PD all-cause mortality were age, serum creatinine, platelet, aspartate aminotransferase, and alkaline phosphatase levels, renal solute clearance rate and normalized protein catabolic rate. These were in agreement with previous studies. The effect of age on risk factors of mortality was shown by a previous study on Iranian pediatric patents on PD by Mujais et al. (15). Also, studies by Gulcan et al. (8) and Herzog et al. (16), on the effects of age as a risk factor for mortality of PD patient support our findings. Risk of mortality was higher in younger children. This association is a reflection of the association observed in the general pediatric population (17). In addition, Holmar et al. (18) showed that serum creatinine and aspartate aminotransferase, normalized protein catabolic rate and appetite were risk factors of all-cause of mortality in PD patient. Lowrie and Lew (19) showed that creatinine level has an inverse relationship with the risk of death. Therefore, our results are consistent with previous studies.

### 4-1. Study Limitations

One of the limitations of this study is the missing data which we attempted to overcome by using Joint models. Another limitation is the possibility of error in data recording. To resolve this limitation, data was carefully monitored prior to the start of analyses.

## 5- CONCLUSION

Our results showed that survival rates of Iranian pediatric PD patients are similar

to other countries. In our study, one-year survival rate of PD patients was 93.6% and five-year survival rate was 76.9%. The most important reasons for the PD all-cause mortality were age at the beginning of PD, serum creatinine, platelet, aspartate aminotransferase, and alkaline phosphatase levels, renal solute clearance rate, and normalized protein catabolic rate. It is suggested that laboratory assessment be continually evaluated in pediatric PD patients to reduce the risk of death.

## 6- CONFLICT OF INTEREST: None.

## 7- ACKNOWLEDGMENTS

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