

## Prevalence and Risk Factors of Technique Failure in Peritoneal Dialysis of Iranian Children and Adolescents

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### Abstract

**Background:** Statistics have shown that the rate of technical failure in peritoneal dialysis (PD) is greater than hemodialysis. In this regard, the present study is aimed to determine the prevalence and risks factors of technique failure of PD in Iranian children using the country's computerized PD data registry system.

**Materials and Methods:** Data of 405 PD patients younger than 20 years old were extracted from Iranian PD registry. The joint models of longitudinal and time-to-event data were used to assess independent risk factors of PD technique failure.

**Results:** PD technique failure occurred in 17.3% of the patients. 1 ng/ml increase in the baseline level of ferritin and 1 mmHg increase in the baseline systolic blood pressure will result in 0.11% (Hazard Ratio [HR]=1.0011; p=0.001), and 1.25% (HR=1.0125; p=0.046) increase in the risk of PD technique failure, respectively. In addition, 1 g/dl decrease in the baseline hemoglobin will cause a 16.25% increase in the risk of PD technique failure (HR=0.8602; p=0.026). Finally, 1 mg/l decrease in the blood urea nitrogen over time after starting PD will result in 1.75% increase in the risk of PD technique failure (HR=0.9829; p=0.006).

**Conclusion:** The findings from this study showed that an increase in ferritin as well as systolic blood pressure at the beginning of PD increase the risk of technique failure. Furthermore, an increase in the hemoglobin level at the beginning of PD as well as an increase in the blood urea nitrogen over time after starting PD have protective impacts on pediatric PD technique failure.

**Key Words:** Dialysis, Pediatrics, Renal Replacement Therapy, Technique failure.

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## 1- INTRODUCTION

Peritoneal Dialysis (PD) is a treatment modality widely used for patients with end-stage renal disease (ESRD) (1). Since its first use for the management of ESRD in 1959 (2), there has been a remarkable improvement in patient survival due to clinical and technological advancements of recent years (3). PD has been the most common initial dialysis method administered to children with ESRD (1). Some of the advantages of PD for children include mobility (in this case, the child can still attend classes in school), less dietary constraints, lower cost, not requirement for steady access to blood, ease of application, and maintenance of residual renal function (4). Despite these merits, its major shortcoming is the possibility of peritonitis, which is higher in children than adults. This drawback may lead to morbidity and mortality (5) as well as technique failure (6).

As defined by Blake (7), technique failure arises when a patient on PD changes to hemodialysis for a period longer than 3 months. It should be noted that this definition excludes patients who underwent successful transplant as well as those died. Patients opt out of PD for several reasons such as peritonitis, ultrafiltration failure, kidney transplantation, and personal reasons. Hence, a reduction can be observed in PD technique survival. Therefore, an improvement in technique survival can significantly contribute to enhancement of PD outcomes among children.

Technique failure is one of the unintended consequences of renal replacement therapy which can deteriorate the prognosis of on-dialysis patients and may result in death if left untreated with another dialysis modality. Despite the advantages of PD over hemodialysis, statistics have shown that the rate of technique failure in PD is greater than hemodialysis (8). Therefore, identifying the underlying causes of

technique failure in PD may prevent hemodialysis with appropriate therapeutic interventions. However, there is insufficient data on the prevalence of technique failure and its risk factors in children. Therefore, this study is aimed to assess the technique failure rate of PD among Iranian children and its risk factors, using the country's computerized PD data registry system.

## 2- MATERIALS AND METHODS

### 2-1. Study design and population

Baseline characteristics and laboratory data of 416 Iranian patients (younger than 20 years old) undergoing PD were extracted from 20 CAPD centers in Iran, and employed in this study. These data were extracted from the Iranian PD registry entered in Hakim software (Electronic Health Record: Pegahsoft, Tehran, Iran). Details of registry and data collection have been reported in previous studies (9, 10). Briefly, the PD registry includes the patients' data from 1995 to February 2018. The data were categorized into 11 general areas including information about the center, baseline characteristics, clinical and laboratory characteristics of patients, patients' treatment and follow-up. The Ethics Committee of Tehran University of Medical Sciences approved the present study protocol.

### 2-2. Outcome

This study was focused on the PD technique failure which is defined as the condition whereby PD was terminated permanently and the patient was listed for hemodialysis or urgent kidney transplantation. Eleven patients were excluded due to incorrect follow-up time or unknown event condition. Thus, analyses were carried out on 405 PD patients up to 20 year-old from 20 CAPD centers throughout Iran.

### 2-3. Statistical Analysis

After describing the 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 important technique failure risk factors. Afterwards, a backward variable selection procedure in multivariate Cox regression (with a P-value < 0.1 for elimination) was used to identify the potential baseline risk factors affecting the technique failure after adjusting for the possible confounders using the R programming language.

R statistical software was also used to analyze the data using joint modeling of longitudinal and time-to-event data. The joint model included two sub models; in the case of our study, the PD patients' follow-up (longitudinal process), and the technique failure of PD patients (event process). It is worth mentioning that in the studies with small (at most 20 to 30%) event percentage (failure), the Cox regression is not the best model for data analysis.

In this regard, cure or joint models have been recommended in the literature. For the specific type of joint model used in our analysis, it is customary to simultaneously model the effect of the potential important baseline risk factors of the event (usually found by Cox regression) on the important predictor of the event like BUN in our study (as a biomarker), and the event (technique failure). It is usually required to use a backward variable selection procedure to find the best set of independent baseline risk factor of the technique failure. As in our study in which the technique failure occurred for only 17.3% of the patients, the joint modeling of patients' follow-up data (with blood urea nitrogen as a biomarker), and the time

to technique failure of PD patients were used to model the data since it was found to be the most accurate. The joint modeling of longitudinal and time-to-event data was composed of two parts including longitudinal and survival sub models. The longitudinal sub model was fitted with mixed effect models in three common ways, which were random intercept, random intercept plus random slope and flexible splines. Thereafter, the Akaike information criterion (AIC), and Bayesian information criterion (BIC) were used to find out the best longitudinal and event sub model. P-value < 0.05 was used to determine significance of the final joint model. The studied variables were standardized to avoid the effect of different unit of measurements.

### 3- RESULTS

Among the studied PD patients (416 subjects), 208 (51.4%) were males. The mean ( $\pm$ standard deviation) age of patients was 8.9 ( $\pm$ 6.4) years. The mean of laboratory variables are presented in **Table.1**. PD technique failure occurred in 17.3% of the patients. Kaplan-Meier survival curve is plotted in **Figure.1**.

The univariate and multivariate Cox regression [Hazard Ratio (HR), and the corresponding 95% Confidence Interval (95% CI)] are also listed in **Table.2**. The analyses showed that serum hemoglobin level (HR=0.881; 95% CI: 0.778 to 0.998; p=0.047), serum blood urea nitrogen (HR=0.990; 95% CI: 0.983 to 0.998; p=0.013), serum ferritin (HR=1.001; 95% CI: 1.0005, 1.002; p=0.007), and systolic blood pressure (HR=1.012; 95% CI: 0.999, 1.024; p=0.007) are the possible independent risk factors for PD technique failure.

**Table-1:** Baseline and laboratory characteristics of the studied patients (n=416).

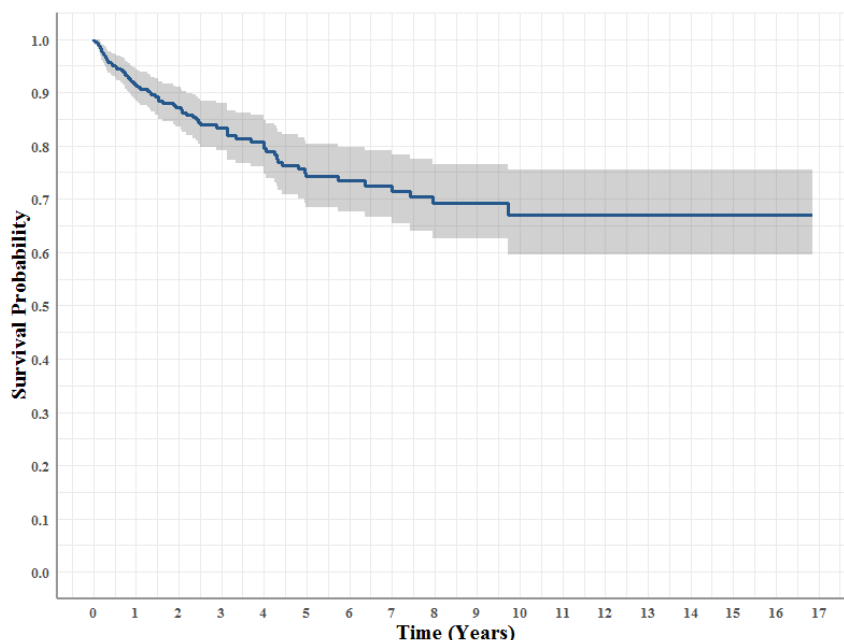
| Variables   | Technique did not fail | Technique failed   |
|---|------------------------|--------------------|
| Gender (%)  |                        |                    |
| Female  | 158 (47.16)            | 39 (55.71)         |
| Male  | 177 (52.84)            | 31 (44.29)         |
| Age   | 8.82±6.39              | 9.54±6.41          |
| Weight  | 46.03±19               | 43.13±22.32        |
| Height  | 128.41±31.83           | 131.94±30.32       |
| Appetite (%)                                      |                        |                    |
| Low   | 32 (9.55)              | 7 (10)             |
| Medium  | 284 (84.78)            | 58 (82.86)         |
| High  | 19 (5.67)              | 5 (7.14)           |
| White blood cell count (Count)                    | 7573.21±2530.77        | 7494.94±1724.82    |
| Hemoglobin (g/dl)                                 | 9.86±1.93              | 9.37±1.81          |
| Creatinine (mg/dl)                                | 6.44±2.52              | 6.34±2.51          |
| Sodium (mEq/l)                                    | 137.68±5.25            | 138.17±5.9         |
| Potassium (mEq/l)                                 | 4.61±0.77              | 4.64±0.76          |
| Phosphate (mg/dl)                                 | 5.38±1.47              | 5.49±1.59          |
| Fasting blood sugar (mg/dl)                       | 112.17±39.76           | 111.33±30.81       |
| Blood urea nitrogen (mg/l)                        | 73.91±35.64            | 65.73±25.22        |
| Calcium (mg/dl)                                   | 8.83±0.96              | 8.7±0.85           |
| Congenital hypothyroidism (ng/ml)                 | 192.62±39.95           | 196.43±52          |
| Triglyceride (mg/dl)                              | 192.1±91.05            | 197.33±122.02      |
| Platelet count (Count)                            | 251743.61±86637.39     | 240572.63±65317.35 |
| Alkaline phosphatase protein (U/l)                | 445.56±321.52          | 407.41±252.09      |
| High density lipoprotein (mg/dl)                  | 42.25±7.15             | 42.23±6.45         |
| High density lipoprotein (mg/dl)                  | 109.42±28.48           | 110.75±33.43       |
| Iron (g/l)  | 82.13±35.01            | 79.16±22.36        |
| Aspartate aminotransferase (U/l)                  | 28.49±33.34            | 25.64±7.86         |
| Alanine aminotransferase (U/l)                    | 28.89±64.99            | 24.48±8.48         |
| Transferrin, total iron-binding capacity (mcg/dl) | 290.43±80.24           | 276.96±51.24       |
| Ferritin (ng/ml)                                  | 347.38±201.91          | 438.54±415.7       |
| Parathyroid hormone (pg/ml)                       | 258.72±170.53          | 256.81±125.21      |
| Albumin (g/dl)                                    | 3.83±0.41              | 3.74±0.37          |
| Erythrocyte sedimentation rate (mm/hr)            | 56.45±21.21            | 62.39±22.39        |
| Urine volume rate (ml/day)                        | 606.21±407.26          | 562.15±373.92      |
| Ultrafiltration rate (ml/day)                     | 855.21±380.32          | 933.88±345.22      |
| Systolic blood pressure (mmHg)                    | 122.1±20.15            | 125.64±20.43       |
| Diastolic blood pressure (mmHg)                   | 75.23±12.19            | 77.04±11.74        |
| Renal solute clearance rate (rCrCl)               | 26.06±18.43            | 23.4±12.11         |
| Peritoneal solute clearance rate (pCrCl)          | 46.81±8.01             | 48.94±6.15         |
| Total solute clearance rate (tCrCl)               | 73.46±21.02            | 76.29±20.65        |
| Glomerular filtration rate (ml/min)               | 2.48±2.04              | 2.49±2.37          |
| Renal solute clearance rate (rKt/V)               | 0.51±0.31              | 0.49±0.28          |
| Peritoneal solute clearance rate (pKt/V)          | 1.62±0.31              | 1.7±0.27           |
| Total solute clearance rate (tKt/V)               | 2.11±0.37              | 2.15±0.4           |
| Normalized protein catabolic rate (g/kg/day)      | 1.11±0.25              | 1.12±0.23          |

**Table-2:** Univariate and multivariate Cox regression results.

| Variables   | Univariate             |         | Multivariate          |         |
|---|------------------------|---------|-----------------------|---------|
|   | HR (95% CI)            | P-value | HR (95% CI)           | P-value |
| Gender (%)  |                        |         | -                     | -       |
| Male  | <i>Reference</i>       |         |                       |         |
| Female  | 1.4756 (0.9204,2.3655) | 0.1062  | -                     | -       |
| Age   | 0.9951 (0.9592,1.0323) | 0.7936  | -                     | -       |
| Weight  | 0.9982 (0.9865,1.010)  | 0.7592  | -                     | -       |
| Height  | 1.0034 (0.9956,1.0113) | 0.3885  | -                     | -       |
| Appetite (%)                                      |                        |         | -                     | -       |
| High  | <i>Reference</i>       |         |                       |         |
| Medium  | 1.2133 (0.6508,2.2618) | 0.5429  | -                     | -       |
| Low   | 0.8192 (0.375,1.7896)  | 0.617   | -                     | -       |
| White blood cell count (Count)                    | 1.000 (0.9999,1.0001)  | 0.974   | -                     | -       |
| Hemoglobin (g/dl)                                 | 0.8891 (0.7897,1.0011) | 0.0521  | 0.881 (0.778, 0.998)  | 0.047   |
| Creatinine (mg/dl)                                | 0.9744 (0.8908,1.0658) | 0.5709  | -                     | -       |
| Sodium (mEq/l)                                    | 1.0008 (0.950,1.0543)  | 0.9767  | -                     | -       |
| Potassium (mEq/l)                                 | 1.133 (0.8496,1.5110)  | 0.3951  | -                     | -       |
| Phosphate (mg/dl)                                 | 1.0819 (0.9203,1.2718) | 0.3401  | -                     | -       |
| Fasting blood sugar (mg/dl)                       | 1.0015 (0.9954,1.0076) | 0.6413  | -                     | -       |
| Blood urea nitrogen (mg/l)                        | 0.9937 (0.9865,1.001)  | 0.0913  | 0.990 (0.983, 0.998)  | 0.013   |
| Calcium (mg/dl)                                   | 0.8399 (0.6516,1.0826) | 0.178   | -                     | -       |
| Congenital hypothyroidism (ng/ml)                 | 1.0023 (0.997,1.0076)  | 0.3955  | -                     | -       |
| Triglyceride (mg/dl)                              | 1.0009 (0.9989,1.0029) | 0.3663  | -                     | -       |
| Platelet count (Count)                            | 1.000 (1.000,1.000)    | 0.4357  | -                     | -       |
| Alkaline phosphatase protein (U/l)                | 0.9993 (0.9984,1.0002) | 0.1232  | -                     | -       |
| High density lipoprotein (mg/dl)                  | 0.9969 (0.9654,1.0295) | 0.85    | -                     | -       |
| High density lipoprotein (mg/dl)                  | 1.0029 (0.9952,1.0106) | 0.4625  | -                     | -       |
| Iron (g/l)  | 0.9967 (0.9888,1.0048) | 0.4262  | -                     | -       |
| Aspartate aminotransferase (U/l)                  | 0.9897 (0.9649,1.0152) | 0.4265  | -                     | -       |
| Alanine aminotransferase (U/l)                    | 0.9996 (0.9907,1.0087) | 0.9362  | -                     | -       |
| Transferrin, total iron-binding capacity (mcg/dl) | 0.9974 (0.9932,1.0016) | 0.2226  | -                     | -       |
| Ferritin (ng/ml)                                  | 1.0012 (1.0006,1.0019) | 0.0002  | 1.001 (1.0005, 1.002) | 0.007   |
| Parathyroid hormone (pg/ml)                       | 0.9994 (0.998,1.0009)  | 0.4427  | -                     | -       |
| Albumin (g/dl)                                    | 0.5607 (0.3239,0.9707) | 0.0388  | -                     | -       |
| Erythrocyte sedimentation rate (mm/hr)            | 1.0107 (1.0017,1.0198) | 0.0201  | -                     | -       |
| Urine volume rate (ml/day)                        | 0.9998 (0.9992,1.0004) | 0.5409  | -                     | -       |
| Ultrafiltration rate (ml/day)                     | 1.0005 (0.9999,1.001)  | 0.098   | -                     | -       |
| Systolic blood pressure (mmHg)                    | 1.0144 (1.0021,1.0269) | 0.0215  | 1.012 (0.999, 1.024)  | 0.058   |
| Diastolic blood pressure (mmHg)                   | 1.0218 (1.000,1.044)   | 0.0499  | -                     | -       |
| Renal solute clearance rate (rCrcl)               | 0.9946 (0.9805,1.0089) | 0.4588  | -                     | -       |
| Peritoneal solute clearance rate (pCrcl)          | 1.037 (1.0033,1.0718)  | 0.0313  | -                     | -       |
| Total solute clearance rate (tCrcl)               | 1.0079 (0.9976,1.0183) | 0.1322  | -                     | -       |
| Glomerular filtration rate (ml/min)               | 1.0276 (0.9207,1.147)  | 0.627   | -                     | -       |

|  |                        |        |   |   |
|--|------------------------|--------|---|---|
| Renal solute clearance rate (rKt/V)          | 0.9702 (0.4609,2.0424) | 0.9366 | - | - |
| Peritoneal solute clearance rate (pKt/V)     | 2.2265 (0.9421,5.2619) | 0.0681 | - | - |
| Total solute clearance rate (tKt/V)          | 1.3261 (0.7257,2.4235) | 0.3588 | - | - |
| Normalized protein catabolic rate (g/kg/day) | 0.9955 (0.3751,2.642)  | 0.9928 | - | - |

CI: Confidence interval; HR: Hazard ratio.



**Fig.1:** Kaplan-Meier survival curve for assessment of technique survival in children on peritoneal dialysis.

Finally, using a backward variable selection procedure in the sub-model of our joint model, it was found that ferritin, hemoglobin, systolic blood pressure, and blood urea nitrogen were the independent risk factors of technique failure (**Table.3**). Furthermore, findings indicated that when all measured variables are held constant, 1 ng/ml increase in the baseline ferritin level will result in 0.11% elevation in the risk of PD technique failure (HR=1.0011; 95% CI: 1.0005 to 1.0017; p=0.001). In addition, 1 g/dl decline in the baseline

hemoglobin level will cause a 16.25% increase in the risk of PD technique failure (HR=0.8602; 95% CI: 0.7534 to 0.9821; p=0.026). Furthermore, 1 mmHg increase in the baseline systolic blood pressure will lead to 1.25% enhancement in the risk of PD technique failure (HR=1.0125; 95% CI: 1.0002 to 1.025; p=0.046). Finally, 1 mg/l decrease in the blood urea nitrogen level over time after starting PD will result in 1.75% increase in the risk of PD technique failure (HR=0.9829; 95% CI: 0.9708,0.9951; p=0.006).

**Table-3:** Independent risk factors of PD technique failure.

| Risk factors            | $\beta$ ( $\pm$ SE)     | HR     | 95% CI          | P-value |
|-------------------------|-------------------------|--------|-----------------|---------|
| Ferritin                | 0.0011 ( $\pm$ 0.0003)  | 1.0011 | (1.0005,1.0017) | 0.001   |
| Hemoglobin              | -0.1506 ( $\pm$ 0.0676) | 0.8602 | (0.7534,0.9821) | 0.026   |
| Systolic blood pressure | 0.0125 ( $\pm$ 0.0062)  | 1.0125 | (1.0002,1.025)  | 0.046   |
| Blood urea nitrogen     | -0.0173 ( $\pm$ 0.0063) | 0.9829 | (0.9708,0.9951) | 0.006   |

CI: Confidence interval; HR: Hazard ratio; SE: Standard error.

#### 4- DISCUSSION

This study was aimed to assess the technique failure rate of PD in Iranian children and its risk factors, using the national PD data registry system. The findings showed that after adjusting for the confounders, the increase in ferritin and systolic blood pressure at the beginning of PD augmented the risk of technique failure; while an enhancement in the hemoglobin level at the beginning of PD as well as an increase in blood urea nitrogen level over time after starting PD exhibited a protective effect on PD technique failure in our studied population. The effects of ferritin, hemoglobin, and systolic blood pressure were considered as baseline while the impact of blood urea nitrogen was taken as a potential longitudinal biomarker of PD technique failure over time. The effect of hemoglobin on mortality of patients undergoing PD was assessed in previous studies. There are conflicting reports on association of serum hemoglobin levels and risk of mortality in patients with PD (11-14). Unfortunately, the association of serum hemoglobin level and outcome of children on PD is less understood. For example, it was shown in a previous study that serum hemoglobin level is not a risk factor of mortality in PD children (10); while in another study, decreased hemoglobin level was associated with an increased risk of hospitalization and mortality in children with PD (8). Correction of hemoglobin level during dialysis was suggested as an indicator of anemia in observational studies (15, 16). However, clinical trials suggested that this hemoglobin modification might worsen the outcome of dialysis patients (17, 18). This disagreement has led studies to provide a target level for hemoglobin. According to these studies, the target hemoglobin level varied between 10 and 12 g/dl (19, 20). The present study showed that in children on PD, decreased level of hemoglobin

increased the risk of technique failure. This finding also demonstrated the importance of further attention to serum hemoglobin levels in children with PD. The present study showed the positive correlation of the systolic blood pressure with an increased risk of technique failure in children with PD. This finding is consistent with the study of Jager et al., who showed that a 10 mmHg increase in systolic blood pressure in adults with PD led to a 22% increased risk of technique failure (21). Another study also reported similar findings (22). Two mechanisms have been suggested for increased systolic blood pressure in ESRD patients: arterial stiffness and fluid overload (23-25). Arterial stiffness increases the systolic blood pressure and decreases diastolic blood pressure. The fluid overload is a common phenomenon in dialysis patients, partly due to anemia. Anemia results in a decrease in osmotic pressure, which in turn results in the fluid flow from the interstitial space into the bloodstream. This increased fluid flow could have detrimental effects on the cardiovascular system leading to mortality and morbidity. However, the role of systolic blood pressure on technique failure seems to be independent of anemia since our multivariate analysis showed that the systolic blood pressure itself is an independent risk factor for technique failure. Serum ferritin is an indicator of iron stored in the body and the guidelines state that its level should be above 200 ng/ml (26, 27). The relationship between serum ferritin and the outcome of PD in children is controversial. In our previous study, we showed no significant relationship between serum ferritin levels and patient survival in children on PD (10). These findings are in line with the study by Tsai et al. (26). The relationship between serum ferritin and technique failure in children has been poorly examined and a few results can be found in this regard. Most of the existing studies addressed the adult population, which have

shown inconsistent results. For example, Kircelli et al., used the univariate analyses and reported the serum ferritin level was the only predictor of technique failure (28); while, Tangri and his colleagues did not observe any relationship (29).

#### **4-1. Study Limitations**

The most important limitation of the present study is the missing data in the registry, which excluded 11 patients from the analysis; although this had very little impact on our findings.

### **5- CONCLUSION**

The present study showed that an increase in both ferritin and systolic blood pressure at the beginning of PD can enhance the risk of technique failure. Furthermore, an increase in hemoglobin level at the beginning of PD as well as an elevation of the blood urea nitrogen level over time after starting PD exhibited protective effects on pediatric PD technique failure.

**6- CONFLICT OF INTEREST:** None.

### **7- ACKNOWLEDGMENTS**

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