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The Importance of Blood Pressure Control in the Survival of Peritoneal Dialysis Patients Using a Multistate Model

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Abstract

Since less attention has been paid to the effect of passing blood pressure states on the survival of peritoneal dialysis (PD) patients, this study aimed to investigate the survival of PD patients with and without hypertension, estimate the probability of hypertension, and determine the influential factors. In this retrospective cohort study, the data of 700 patients visiting dialysis centers from all provinces of Iran from 1997-2009 were analyzed. For data analysis, the multistate survival model was used. The median survival time (months) and five-year survival were 75% and 56%, respectively. Males had a higher probability of hypertension (63%) than females (52%). The risk of death in normotensive patients increased with age and fast blood sugar (FBS) (age: HR = 1.02, p-value <0.001; FBS: HR = 1.03, p-value = 0.034) and decreased with increasing protein albumin (albumin: HR = 0.60, p-value = 0.015). When experiencing hypertension, the death risk increased with age (age: HR = 1.03, p-value <0.001); also, higher serum albumin and blood urea nitrogen (BUN) had a protective effect against mortality (albumin: HR = 0.66, p-value = 0.038; BUN: HR = 0.99, p-value = 0.014). Paying attention to age, obesity, and blood sugar in PD patients seems necessary.

Keywords: blood pressure, dialysis, hypertension, Multistate Model

Introduction

End-stage renal disease (ESRD) means an irreversible decline in kidney function that is severe enough to be fatal if dialysis or transplantation is not performed. Kidney failure or its reduced function causes a maladaptive process, including fluid retention. Among people living with ESRD, fluid retention significantly leads to hypertension, ventricular dysfunction, and additional cardiovascular events.[1] Several studies revealed that diabetes, high blood pressure, and glomerular disease are the major causes of ESRD.[2,3] Also, the ESRD prevalence is higher in cardiac patients and the elderly. Therefore, the growth of the elderly population and the increasing number of diabetic patients in recent years may allow the ESRD prevalence to rise in the future.[2,3]

Peritoneal dialysis (PD) is an attractive and cost-effective treatment for kidney failure, introduced in the late 1970s.[4] The home-based nature and flexibility of this method has increased its use compared to hemodialysis in many parts of the world.[5] Although the mortality rate of patients undergoing outpatient PD treatment has decreased in recent years, their survival rate is still a matter of concern, in which even after 10 years, the probability of survival of these patients may reach lower than 11%.[6]

One of the crucial issues in treating kidney disease is controlling blood pressure. High blood pressure is both a cause and a consequence of chronic kidney disease (CKD), and it affects most CKD patients.[7] The systematic review and meta-analysis studies showed a high prevalence of hypertension in kidney patients. The combined prevalence in both CKD and ESRD patients is estimated at 23%, and the prevalence in CKD patients is estimated at 32%.[8,9] Moreover, in Iran, the prevalence is estimated at 35% for kidney disease patients.[10]

Hypertension has been recognized as the most common comorbidity for PD patients, and the risk of death among patients with hypertension is higher than among those without hypertension. A study on survival concluded that blood pressure was a predictor of death among dialysis patients, and PD patients with high blood pressure had shorter

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survival compared to others.[11] In addition, increased blood pressure due to increased serum sodium concentration causes cardiac complications and subsequently shortens the survival time of dialysis patients.[12]

Although many studies have introduced risk factors for hypertension (e.g., diabetes, age), the effectiveness of prevention requires two factors: first, accurate prediction of the onset of hypertension, and second, identification of transition patterns between different states of blood pressure.[13] However, in the existing literature, the intermediate between the normal and diseased states has not been well studied. The natural progression of high blood pressure is a dynamic process, and people living with CKD may experience different stages of its progression over time. Therefore, observing its natural progression is necessary for early diagnosis and prevention.[14]

The low rate of PD patients' survival has led many studies to determine its causes and generated a large amount of data.[15-16] Accurate and efficient methods are required for effective use of the data. Since ESRD patients might experience different states of blood pressure before death, hypertension could be considered an intermediate condition accelerating death.[17-18] Risk factors for death may differ from risk factors for intermediate outcomes. Ignoring the intermediate states and the time elapsed until they occur may lead to inaccurate results. Therefore, a multistate survival model is used to examine patient survival rates by considering a correlation between intermediate states of the disease.[19]

Despite the importance of blood pressure control for kidney patients, examining the survival of dialysis patients from the hypertension aspect as an intermediate state has received less attention. Therefore, this study aimed to examine the probability of survival of PD patients with or without passing through the hypertensive state, calculate the probability of transitioning to a hypertensive state before death and identify influential factors to PD patients' survival passing through blood pressure states. The aforementioned cases were still ambiguous for PD patients, and the multistate model was used in this study to solve these problems.

Method

This retrospective cohort study obtained data from the Iranian peritoneal dialysis registry project.[20] The information on patients with kidney failure who had visited the 46 dialysis centers from all Iranian provinces was recorded. The patients were given the necessary information to participate in the study, and those with full consent were included. Each person was identified by only one ID; other personal information was kept confidential and could not be extracted.

For data collection, several forms in the same electronic format were sent to the dialysis centers, and the completed forms were returned to the main registry center in Alborz Province, Iran. The data could be extracted after obtaining approval from the relevant officials. The executive and operational duties of this plan were approved by the Department of Organ Transplantation and Special Diseases, Deputy for Medicare, Iranian Ministry of Health in 2004. Such duties accommodate coordination between related organizations, which include research centers and the Nephrology Association, planning for holding meetings and training the technicians, designing data extraction software, confirming data quality, etc.

The patients were followed up from 1997 to 2009. The minimum follow-up time was five days, and the maximum was 12 years. This study examined the data of patients visited at least twice. The data collection forms included the demographic, clinical, and laboratory characteristics of the patients, as well as their treatment and follow-up process. In this study, basic characteristics, such as sex (male/female), age (year), weight (kg), height (m), comorbidity (yes/no), triglycerides/Trg (mg/dL), fast blood sugar/FBS (mg/dL), protein albumin (g/dL), serum sodium/Na (mg/L), potassium/K (mol/L), creatinine/Cr (mg/dL) and blood urea nitrogen/BUN (mg/dL) were analyzed considered as the independent variable. Time (months) was considered right-censored for patients who were still alive or whose conditions were unclear until the last follow-up.

To observe the patients' conditions, their systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured and recorded at each visit. A mercury sphygmomanometer was used to measure blood pressure after a 10- to 20-minute rest period. To record blood pressure, each patient was measured twice, and the average of the two times was calculated. A patient's blood pressure, according to guidelines by medical associations, consists of four stages: normal (SBP <120 mmHg and DBP <80 mmHg), elevated (SBP in the range of 120–129 mmHg and DBP <80 mmHg), hypertension stage I (SBP in the range of 130–139 mmHg or DBP in the range of 80–89 mmHg, and hypertension stage II (SBP ≥140 mmHg or DBP ≥90 mmHg).[21]

The inclusion criteria included those aged >18 years and prescribed peritoneal dialysis therapy. Exclusion criteria included kidney transplant or hemodialysis. In addition, people whose information was incomplete or did not want to continue the treatment were excluded from the study. In this study, it was possible to access the data of 1,800 patients. Among these patients, 700 patients had normal or elevated blood pressure. The rest of the patients either did not have normal blood pressure or had incomplete information and were excluded from the study. Hence, the clinical changes of 700 patients with normal or elevated states were observed. For data analysis, the effect of the mentioned independent

variables on the survival of patients with or without passing through hypertensive status was determined.

Considering that dialysis patients might experience different blood pressure conditions before they died, and these interdependent conditions affected their time of death, a multistate model was required to examine the survival rate. Therefore, multiple stages of blood pressure were used to build a three-state survival model so that state 1 included normal or elevated blood pressure, state 2 included hypertension (stage I or II), and death was considered as state 3 (absorbing state). The graph of this model is shown in Figure 1.

In this model, the state change is considered an event, and the time until the occurrence of each event is calculated. Multistate models can be used for the transition from state s to r, ($r \neq s$) with the aid of the Cox proportional hazards model and formulated as on Formula 1. The level of 5% was considered statistically significant, and analysis was done using a free version of R 4.2.2 software and the mstate statistical package.

Results

Of the examined 700 dialysis patients, 423 (60.4%) were females, and the rest were males. The youngest person aged 20 years, and the oldest aged 87 years. The mean body mass index (BMI) of all patients was 23.02±4.96. Also, 583 (83.3%) people had at least one comorbidity. Of the total population studied, 400 (57.14%) people had hypertension, while 278 (39.71%) people had experienced death (directly from the normal state or passing through the hypertensive state). The details of patients' characteristics based on the occurrence of the event can be seen in Table 1.

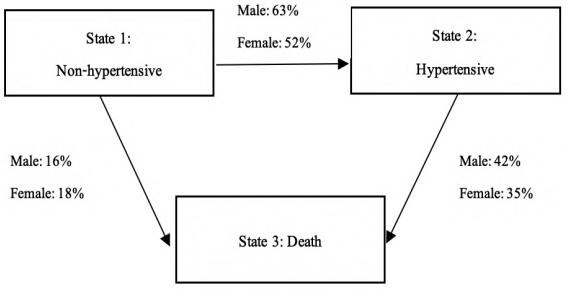

Figure 1. Diagram of Transitions for Peritoneal Dialysis Patients

$$q_{rs}(t) = q_{rs,0}(t)\, exp(\boldsymbol{X}_{rs}{}^{T}\boldsymbol{\beta})$$

Notes:
$q_{(rs,0)}$ = the baseline risk
X = vector of predictor variables
β^{T}_{rs} = the unknown parameters

Formula 1. Hazard of Transition Model

Table 1. Main Characteristics of Peritoneal Dialysis Patients by Blood Pressure States

Variable	Category	Overall	Non-hypertensive	Hypertensive	Survivor	Dead
Age (Mean±SD)		50.70±16.35	50.28±16.74	50.98±16.10	64.70±15.67	56.52±15.59
Sex, n (%)	Male	277 (39.6)	101 (33.66)	176 (44.0)	157 (37.20)	120 (43.16)
	Female	423 (60.4)	199 (66.34)	224 (56.0)	265 (62.80)	158 (56.83)
BMI (Mean±SD)		23.02±4.96	22.52±5.42	23.35±4.60	22.99±5.12	23.06±4.73
Comorbidity, n (%)	Yes	583 (83.3)	235 (83.8)	348 (83.3)	329 (79.3)	254 (89.1)
	No	117 (16.7)	47 (16.7)	70 (16.7)	86 (20.7)	31 (10.9)
FBS (Mean±SD)		124.26±62.91	124.23±67.28	124.28±59.87	117.93±54.60	133.48±72.47
Trg (Mean±SD)		175.77±92.26	173.17±97.43	177.52±88.67	173.16±81.42	179.57±106.12
K (Mean±SD)		4.64±0.75	4.62±0.70	4.65±0.78	4.67±0.75	4.59±0.75
Na (Mean±SD)		139.32±3.91	139.19±3.89	139.41±3.92	139.38±3.82	139.24±4.05
Cr (Mean±SD)		6.51±2.76	6.49±2.64	6.51±2.83	6.65±2.67	6.29±2.86
Albumin (Mean±SD)		3.97±0.43	3.71±0.44	3.84±0.42	3.83±0.47	3.73±0.36
BUN (Mean±SD)		77.97±40.89	77.56±39.57	78.26±41.79	80.21±41.55	74.71±39.75

Notes: SD = Standard Deviation, BMI = Body Mass Index, FBS = Fasting Blood Sugar, Trg = Triglycerides, K = Potassium, Na = Sodium, Cr = Creatinine, BUN = Blood Urea Nitrogen.

According to Table 1, to compare patients in terms of blood pressure, the amounts of BUN, Albumin, Cr, Trg, BMI, and age among patients with high blood pressure are higher than others. The percentage of males in the hypertensive group (44%) was higher than the non-hypertensive group (33%). In comparison, the percentage of females in the non-hypertensive group (66%) was higher than the hypertensive group (56%). People in two groups of blood pressure were similar in having or not having comorbidity.

The comparison of patients in terms of death showed that BUN, Albumin, Cr, Na, K, and age were lower for those who died than those who survived. However, Trg and FBS were higher for those who died than those who survived. Also, males had the highest percentage of deaths (43%), while females had the highest percentage among survivors (62%) (Table 1). The median overall survival time of patients was 75 months. The patient's survival at one-year, five-year, and ten-year intervals was 93%, 56%, and 37%, respectively. The median time until the occurrence of hypertension was 59.46 months. The probability of hypertension after one, five, and ten years of follow-up was 33%, 69%, and 87%, respectively.

Frequency of Transitions between Defined Blood Pressure States and Death

The number and percentage of people whose blood pressure had or had not changed by the end of the study varied among the male and female populations (Figure 1). Of 277 males in non-hypertensive states, 176 (63%) had reached hypertensive state, 46 (16%) had died, and 55 (20%) had not experienced any change in blood pressure state. Of 176 males experiencing high blood pressure, 102 (58%) had no change in condition, and 74 (42%) had died. In general, in the male population, the number of deaths was 120 (43%). In the female population, out of 423 females in the non-hypertensive state, 224 (52%) had reached a hypertensive state, 80 (18%) had died, and 120 (28%) remained in the non-hypertensive state. Of 244 females experiencing high blood pressure, 146 (65%) remained in such condition, and 78 (35%) died. A total of 158 (14%) people died in the female population. To conclude, the percentage of deaths among patients experiencing high blood pressure was higher for males than for females. Also, males had a higher probability of high blood pressure compared to females.

Risk Factors for High Blood Pressure or Death

The results of the Cox regression model on the risk of high blood pressure or death in Table 2 show that the risk of high blood pressure increases by 4% with one kg/m^2 increase in BMI. Also, the risk increases by 2% with one g/dL increase in albumin. The risk of death without experiencing hypertension increases by 2% with a one-year increase in age and by 3% with a one mg/dL increase in FBS, while it decreases by 40% with a one g/dL increase in albumin. The risk of death with hypertensive experience increases by 3% with a one-year increase in age, while it decreases by 34% and 1% with a one g/dL increase in albumin and one mg/dL increase in BUN, respectively. No significant effects are seen for other variables with no asterisk in the Table 2.

Predicting the Probability of Transition to High Blood Pressure or Death Using the Cox Model

The transmission risk, which considers the patients' significant conditions, is shown in Figures 2 and 3. According to Figure 2, the cumulative risk of transition from a hypertensive state to death is greater than the risk of transition

Table 2. Effects of Covariates on Transition Intensity for Blood Pressure States

Variable	Non-hypertensive→Hypertensive		Non-hypertensive→Death		Hypertensive→Death	
	HR (p-value)	95% CI	HR (p-value)	95% CI	HR (p-value)	95% CI
Age	1.00 (0.567)	(0.99–1.01)	1.02 (<0.001)*	(1.01–1.03)	1.03 (<0.001)*	(1.02–1.04)
Sex; male	1.03 (0.754)	(0.84–1.26)	0.78 (0.213)	(0.67–1.00)	1.14 (0.412)	(0.90–1.35)
BMI	1.04 (0.010)*	(1.01–1.04)	0.98 (0.383)	(0.97–1.01)	0.98 (0.276)	(0.97–1.01)
Comorbidity; yes	1.18 (0.241)	(0.90–1.35)	0.76 (0.270)	(0.55–1.22)	0.67 (0.073)	(0.45–1.00)
Cr	0.97 (0.226)	(0.96–1.00)	0.97 (0.437)	(0.91–1.03)	1.03 (0.420)	(0.96–1.08)
Na	0.97 (0.814)	(0.98–1.02)	0.99 (0.708)	(0.95–1.03)	1.02 (0.330)	(0.98–1.06)
FBS	0.99 (0.637)	(0.99–1.00)	1.03 (0.034)*	(1.01–1.05)	0.99 (0.586)	(0.99–1.00)
Trg	0.99 (0.643)	(0.99–1.00)	0.99 (0.923)	(0.99–1.00)	1.00 (0.148)	(0.99–1.00)
Albumin	1.02 (0.014)*	(1.01–1.49)	0.60 (0.015)*	(0.41–0.90)	0.66 (0.038)*	(0.55–0.82)
K	0.95 (0.486)	(0.83–1.11)	0.84 (0.238)	(0.74–1.10)	1.00 (0.960)	(0.82–1.23)
BUN	1.00 (0.299)	(0.99–1.00)	1.00 (0.344)	(0.99–1.00)	0.99 (0.014)*	(0.99–0.99)

Notes: CI = Confidence Interval, HR = Hazard Ratio

* = Statistical Significance, BMI = Body Mass Index, Cr = Creatinine, Na = Sodium, FBS = Fasting Blood Sugar, Trg = triglycerides, K = Potassium, BUN = Blood Urea Nitrogen.

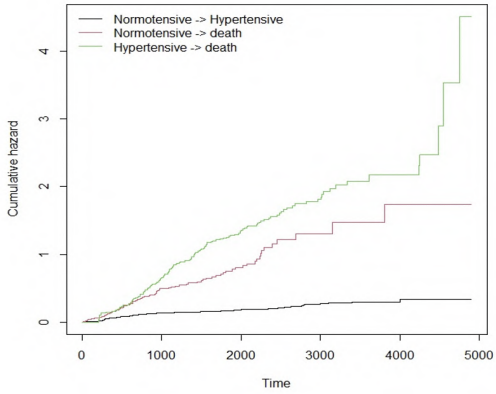

Figure 2. Cumulative Hazard for Three Transitions in Peritoneal Dialysis Patients

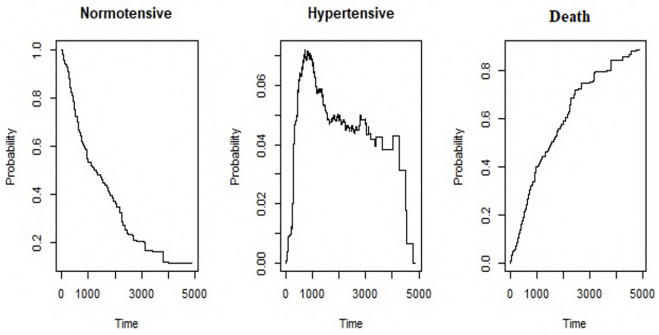

Figure 3. Patient-specific Transition Probability from State 1 in Peritoneal Dialysis Patients

Table 3. Expected Length of Stay in Each States

	In Normotensive	In Hypertensive
From normotensive	57.56 months	6.88 months
From hypertensive	-	49.92 months

from a non-hypertensive state to death. Also, the risk of these transitions is higher than the transition from a non-hypertensive state to a hypertensive state. According to Figure 3, the probability of remaining in a non-hypertensive state decreases over time. Moreover, the probability of transitioning to a hypertensive state increases up to 30 months and then decreases. The probability of death in a non-hypertensive state increases over time.

Duration of Remaining in Different Blood Pressure Status

The expected lengths of remaining in each defined blood pressure state are given in Table 3. According to this table, the time to remain in the normotensive state (57.56 months) is longer than that in the hypertensive state (49.92 months), which means that patients with hypertension experience a shorter life.

Discussion

Previous studies have shown that the prevalence of hypertension in Iran (48.2% in the adult population) is increasing.[22-23] In addition, blood pressure instability and the need to control it is a significant problem for kidney patients.[24] Therefore, paying attention to the pattern of a transition to a hypertensive state and its influential factors could be a basis for successful control of blood pressure and ultimately increase the survival of dialysis patients. In this study, a three-state survival model was used considering the blood pressure status to observe the influential factors to the Iranian PD patients' survival. Also, the probability of transitioning to a hypertensive state and the survival time with the hypertension experience were reported for the mentioned patients.

This study found some basic new points. The death risk of experiencing hypertension was higher than the risk of experiencing hypertension itself. Over time, the probability of high blood pressure increased until the first three years of dialysis and then decreased. Women were more likely to remain in their current blood pressure status (normotensive or hypertensive state) than men. The probability of death without high blood pressure experience was higher for women than men. In addition, the transition to hypertension, as well as the probability of death with the hypertension experience, was higher in men.

This study revealed that albumin and BMI were among the influential factors in the transition from normotension to hypertension status. The results on BMI were consistent with the study on the American working population,[25] and Chinese adults.[26] In the mentioned studies, the three-state model of blood pressure was used, considering hypertension as an absorbing state, but the death risk was not examined. Therefore, those studies were incomparable with the present study in terms of factors affecting death.

Previously, the role of obesity in causing kidney damage and increasing blood pressure has been proven.[27] Obesity, accompanied by increased visceral fat, is a major cause of high blood pressure. The cause of high blood pressure due to obesity is renal sodium reabsorption. Also, because of the compression of the kidney by the perineal fat, the plasma volume increases and leads to consequences, such as impaired baroreceptor and chemoreceptor reflexes and an increase in renal sympathetic nervous activity, and then blood pressure increases.[28]

Albumin is one of the most important blood plasma proteins, which plays an important role in maintaining blood oncotic pressure. Hypoalbuminemia increases the risk of cardiovascular diseases.[29] Few studies have been done on the relationship between serum albumin and blood pressure in PD patients. The permeability of the peritoneal membrane is an important factor in the exchange of fluids and solutes between the peritoneal and blood circulation in PD patients. Hypoalbuminemia might result from increased dialytic albumin loss and relative hemodilution for insufficient ultrafiltration caused by high dialysate glucose absorption.[30] The results of a study on the survival of PD patients showed that lower serum albumin leveled up the risk of patients' death.[31] The statistical model used, the follow-up time, and the amount of albumin and BUN in patients differed from this study.[31] In the mentioned study, the exact level of low serum albumin was also not determined in the analysis.[31]

This study observed the role of blood pressure before the possible occurrence of death. It showed that PD patients might experience increased serum albumin and blood pressure before death. Also, the serum albumin was analyzed as a continuous variable, and more studies are needed to determine a cut-off point for its high or low level. The difference in the results of this study from the previous studies might be due to differences in nutritional conditions, as serum albumin is a measure of the patient's nutritional status. Another important point was a systemic inflammation (e.g., C-Reactive Protein (CRP)) condition for CKD patients, as the low level of serum albumin might have interacted with CRP. The death risk evidently increased in kidney patients with low serum albumin who had high CRP, while the death risk did not increase for these patients with normal CRP.[32] However, this study did not examine this point due to a lack of information. The albumin level in kidney patients is possibly affected by other unknown factors. Therefore, more studies are needed to express an opinion on albumin.

In terms of influential factors to the PD patients' survival, in this study, the death risk with or without passing through the hypertensive state was examined. At the same time, this issue was not addressed in previous studies. Based on the findings of this study, increasing age and FBS increased the risk of death in patients with normal or high blood pressure status. In addition, in case of experiencing high blood pressure, increasing age leads to an increased risk of death.

While, the albumin and BUN indices had a protective role against death, although the role of BUN may be negligible due to its decreasing effect of one percent. Compared to previous studies, the finding of this study on the role of aging as an accelerating factor was in line with studies by Kang et al.[33] on the survival of PD patients and the protective role of albumin, as well as Cheng et al.[34] on the survival of diabetic PD patients.

Regarding the role of blood sugar levels, previous studies found that diabetes increased the risk of death in PD patients.[35-36] To examine the effects of aging in increasing the risk of death in PD patients, the weakening of kidney function in old age could be highlighted.[35] Moreover, elderly patients commonly have more comorbidities, which leads to a shorter life span.[36]

Prior studies have specifically focused on PD or hemodialysis diabetic patients; in this context, a study by Afghahi et al.[37] on the survival of diabetic patients receiving PD could be referred to, emphasizing that the HbA1c coefficient of variation >2.83 independently increased the risk of death threefold. This study had similar results to the previous study on FBS. One of the causes of an increase in the risk of death among diabetic and dialysis patients was glycemic change.[38] Such instability could occur for a change in the dialysis regime or absorption of a large amount of glucose from the dialysate. Glucose fluctuation might lead to oxidative stress and dysfunction of endothelial cells and damage to them, thereby enhancing the risk of death.[39]

A strength of this study was that it dealt with the survival of PD patients according to their blood pressure changes as a factor of interest. In other words, the risk of death and its influential factors were compared by passing through the high blood pressure condition and also without experiencing it. Also, using multistate survival and Markov models provided powerful data analysis and, subsequently, more accurate results. The limitation of this study was that although some patients might have comorbidities and were taking relevant medications, the effect of taking medication was not considered due to a lack of data.

Conclusion

In the patients receiving PD, the probability of high blood pressure and death is higher for men than women. The BMI and serum albumin are the predictors of hypertension. Increased blood sugar and age enhance the risk of death,

and albumin plays a protective role against death. If the hypertensive state is reached, serum albumin and BUN may play a protective role against death. The probability of experiencing hypertension decreases over time, which is lower compared to the probability of death without experiencing hypertension. The duration of remaining in a non-hypertensive state is longer than in a hypertensive state, and the risk of death rises when a hypertensive state is reached. Increasing age, blood sugar, and obesity can be a warning for the occurrence of hypertension and death. Therefore, it seems necessary to pay attention to these factors in addition to blood pressure control in PD management.

Abbreviations

ESRD: End-stage Renal Disease; PD: Peritoneal Dialysis; CKD: Chronic Kidney Disease; FBS: Fast Blood Sugar; BUN: Blood Urea Nitrogen; SBP: Systolic Blood Pressure; DBP: Diastolic Blood Pressure; BMI: Body Mass Index; SD: Standard Deviation, HR: Hazard Ratio.

Ethics Approval and Consent to Participate

Participation in this study was voluntary, and participants were provided with informed written consent. Ethical approval was obtained from the Research Ethics Committee of the Faculty of Public Health, Tehran University of Medical Sciences (Ethical approval number: IR.TUMS.SPH.REC.1401.250).

Competing Interest

The authors declared that there are no significant competing financial, professional, or personal interests that might have affected the performance or presentation of the work described in this manuscript.

Availability of Data and Materials

Data used in this study are available from the corresponding author upon reasonable request.

Authors' Contribution

HN and MH were responsible for conceptualization and methodology. MY collected data and investigated. HN wrote the original draft. ARF, HN, and MSY critically reviewed the manuscript. MH supervised this study. All authors read and approved the final manuscript.

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