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Original Research

Factors Associated with Long-Term Survival in Maintenance Hemodialysis Patients: A 5-Year Prospective Follow-Up Study

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Abstract

Objectives: In addition to an increase in the prevalence of dialysis treatments for end-stage renal disease worldwide, the mortality rates among patients on maintenance hemodialysis remain higher than that of the general population. This study aims to evaluate factors associated with long-term survival in stable maintenance hemodialysis patients.

Methods: A total of 100 patients initiating hemodialysis by February 2013 were included in this prospective cross-sectional 5-year follow-up study. Data on patient demographics, anthropometric-nutritional parameters, systolic and diastolic blood pressure levels, and hemodialysis parameters, including etiology of kidney failure, hemodialysis duration, peritoneal dialysis history, relative interdialytic weight gain (RIDWG), and Kt/V, were recorded.

Results: Overall 5-year survival rate was 56.6%. The 5-year survival rate was higher in patients with younger age (71.4% below median vs. 42.0% above median, p=0.023), lower systolic (63.3 vs. 50%, respectively, p=0.005) and diastolic (62.5 vs. 51.0%, respectively, p=0.02) blood pressure levels, higher Kt/V (46.9 vs. 66.0%, respectively, p=0.044), lower RIDWG (54.0 vs. 32.7%, respectively, p=0.026), and lower serum leptin levels (63.3 vs. 50.0%, respectively, p=0.047). Cox-regression analysis revealed that only systolic blood pressure (B = 1.081, 95% CI, 0.152 to 0.756, p=0.08) was a significant risk factor for poor survival.

Conclusion: Our findings revealed pre-dialysis systolic blood pressure as the sole risk factor for poor long-term survival in stable maintenance hemodialysis patients. Malnutrition-inflammation, measures of nutrition, inflammation, and anemia had no significant impact on long-term survival.

Keywords: Blood pressure, end-stage renal disease, hemodialysis, survival

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In addition to increase in the prevalence of dialysis treatments for the end-stage renal disease (ESRD) worldwide, the mortality rates among patients on maintenance hemodialysis remain higher than that of general population, despite the continuous improvements of dialysis technology.[1-6]

Accordingly, efforts to improve survival and quality of life in hemodialysis patients have gained increasing importance in nephrology practice.[3-7] Among the various factors suggested to contribute to high mortality rates in ESRD patients on hemodialysis (i.e., demographic profile, infection, poor nutritional status, and older age), cardiovascular disease (CVD) is considered the main cause of death.[5,6,8-10]

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However, mortality in hemodialysis patients remains debated, given the contradictory findings related to association of conventional cardiovascular risk factors (i.e., blood pressure, body mass index [BMI], and serum cholesterol) to the outcomes in the dialysis population (i.e., reverse epidemiology), as well as contribution of some other factors such as malnutrition and inflammation besides the classical risk factors to prognosis in hemodialysis patients.[11-14] Moreover, the prognostic factors have been suggested to differ in respect to their effect on long-term versus short-term survival in hemodialysis patients.[4] Hence, a need for further studies to investigate the relationship between potential risk factors and all-cause/CVD-related mortality in patients undergoing hemodialysis has been emphasized.[4,6,11,14]

Serum albumin is known as the most powerful marker of survival.[15] However, there are several biomarkers may influence the survival of patients undergoing hemodialysis such as parathyroid hormone (PTH), tumor necrosis factors, C-reactive protein (CRP), and leptin.

The study was, therefore, designed to assess the long-term survival in stable maintenance hemodialysis patients in relation to potential prognostic factors through a 5-year prospective follow-up analysis.

Methods

Study Population

A total of 100 patients initiating maintenance hemodialysis by February 2013 were included in this single-center cross-sectional prospective study. Medical records of all consecutive hemodialysis patients starting from February 2013 were reviewed if they had complete baseline data and had been on hemodialysis for at least 1 year, while clinically unstable patients with active cardiovascular or infectious diseases, malignant disease, and liver disorders were excluded from the study. Patients were followed up until date of censoring, which was January 31, 2018, transfer to peritoneal dialysis, kidney transplantation, or death.

The study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the Sisli Etfal Training and Research Hospital Ethical Committee (on October 9, 2012 with number of 199) along with the permission for the use of patient data for publication purposes.

Study Parameters

Demographical data such as age or gender, anthropometric-nutritional parameters (malnutrition inflammation score [MIS], triceps skin fold thickness, and BMI), systolic blood pressure (SBP) and diastolic blood pressure levels, and hemodialysis parameters, including etiology of kidney failure, hemodialysis duration, peritoneal dialysis history, relative interdialytic weight gain (RIDWG), and Kt/V, were recorded in each patient. Laboratory investigation included hemoglobin, platelet-to-lymphocyte ratio, neutrophil-to-lymphocyte ratio, PTH, albumin, prealbumin, tumor necrosis factor-alpha, high sensitivity-CRP, CRP, and leptin. Blood pressures were measured in the second session of the week; blood samples were withdrawn after an overnight fasting in the second session of the week. Serum TNF-alpha level measured by electrochemiluminescence assay (Anogen, Mississauga, Ontario, Canada), serum leptin levels by enzyme-linked immunosorbent assay using the Human Leptin Elisa Kit (Cusabio). Kaplan–Meier survival analysis was performed to determine 5-year survival rates in the overall study population as well with respect to cut-off values of study parameters in two subgroups in accordance with median values. Cox regression analysis was also performed to determine risk factors for poor survival.

Hemodialysis

High-flux membranes were used for all patients in the hemodialysis. Patients' routine laboratory parameters were monitored and controlled in accordance with established protocols. Recombinant human erythropoietin and intravenous iron were prescribed to keep hematocrit within the range of 30–36% URR and Daugirdas formula for Kt/V which were used once a month during the study period to assess the dose of dialysis, with a goal of Kt/V greater than or equal to 1.4.

MIS

Malnutrition-inflammation status of patients defined with a validated tool, the MIS. MIS has 10 components, each with four levels of severity, from 0 (normal) to 3 (very severe). The sum of all components ranges from 0 (normal) to 30 (severely abnormal) and a higher score reflects a more severe degree of malnutrition and inflammation.[16]

Statistical Analysis

Statistical analysis was made using IBM SPSS Statistics for Windows, version 22.0 (IBM Corp., Armonk, NY). Survival analysis was made through Kaplan–Meier analysis and comparisons were made through Log-Rank test. Correlates of survival were determined through Cox-Regression analysis. Data were expressed as median (interquartile range) and percent (%) where appropriate due to the study group size. $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics and Laboratory Findings

Median patient age was 53 years (39.5 to 67) and males

composed 53% of the study population. Hypertension (23%) and diabetes mellitus (18%) were the two most common primary diagnoses in hemodialysis patients. The median duration of hemodialysis was 53.5 months (18.3–104.8), while median RIDWG and Kt/V values were 4.7% (3.6–1.8) and 1.6 (1.4–1.8), respectively (Table 1).

Median levels for serum albumin, CRP, and leptin were 3.9 g/dL (range, 3.7–4.1), 11 mg/L (range, 5.3–24), and 6.1 pg/ml (range, 1.8–15.25), respectively. Other laboratory findings related to hemogram and blood biochemistry analysis are summarized in Table 1.

The 5-year Overall Survival Rates According to Study Parameters

Overall, 1-year, 3-year, and 5-year survival rates were 91.0%, 73.7%, and 56.6%, respectively. Comparison of below median versus above median values revealed higher 5-year survival rate in patients with younger age (71.4% below median vs. 42.0% above median, p=0.023), lower systolic (63.3 vs. 50%, respectively, p=0.005) and diastolic (62.5 vs. 51.0%, respectively, p=0.02) blood pressure levels, higher Kt/V (46.9 vs. 66.0%, respectively, p=0.044), and lower RIDWG (54.0 vs. 32.7%, respectively, p=0.013) and lower serum leptin levels (63.3 vs. 50.0%, respectively, p=0.047) (Table 2).

Cox Regression Analysis for Risk Factors of Poor Survival

Cox-regression analysis revealed that only SBP (B=1.081, 95% CI, 0.152 to 0.756, p=0.008) was a significant risk factor for poor survival (Table 3).

Table 1. Baseline characteristics and laboratory findings

Patient demographics	
Age (years), median (interquartile range)	53 (39.5–67)
Gender (male), %	53
Anthropometric-nutritional parameters	
Body mass index (kg/m^2), median (interquartile range)	23.02 (19.95–25.75)
Triceps skin thickness (mm)	13 (10–18)
Malnutrition inflammation score	6 (4–8)
Systolic blood pressure (mmHg), median (interquartile range)	120 (100–130)
Diastolic blood pressure (mmHg), median (interquartile range)	80 (60–80)
Hemodialysis parameters	
Etiology of kidney failure, %	
Unknown	32
Hypertension	23
Diabetes mellitus	18
Polycystic kidney disease	7
Glomerulonephritis	6
Pyelonephritis	6
Other	8
Hemodialysis duration (months), median (interquartile range)	53.5 (18.3–104.8)
Peritoneal dialysis history before hemodialysis (positive), %	4.1
Relative interdialytic weight gain (%), median (interquartile range)	4.7 (3.6–5.7)
Kt/V, median (interquartile range)	1.57 (1.4–1.8)
Laboratory findings, median (interquartile range)	
Hemoglobin (g/dL)	10.8 (9.5–11.5)
Neutrophil-to-lymphocyte ratio	0.021 (0.017–0.027)
Platelet-to-lymphocyte ratio	135.3 (100.4–190.0)
Parathyroid hormone (pg/mL),	363.5 (244.3–697.3)
Albumin (g/dL)	3.9 (3.7–4.1)
Prealbumin (g/dL)	27.8 (23.9–32.8)
High sensitive C-reactive protein (mg/L)	8.0 (1.9–19.2)
C-reactive protein, median (mg/L)	11 (5.3–24)
Tumor necrosis factor-alpha (pg/mL)	21 (17.3–25.8)
Leptin (pg/ml)	6.1 (1.8–15.25)

Table 2. The 5-year overall survival rates according to study parameters

Variables	5-year survival rate, %		p
	Below median	Above median	
Patient age	71.4	42.0	0.023
Body mass index	59.2	54.0	0.219
Systolic blood pressure	63.3	50.0	0.005
Diastolic blood pressure	62.5	51.0	0.02
Hemodialysis parameters			
Relative interdialytic weight gain	54.0	32.7	0.013
Kt/V	46.9	66.0	0.044
Triceps skin fold thickness	52.2	60.4	0.908
Malnutrition inflammation score	69.4	44.0	0.104
Laboratory findings			
Hemoglobin	59.2	54.0	0.938
Neutrophil-to-lymphocyte ratio	56.6	N/A[a]	–
Platelet-to-lymphocyte ratio	65.3	48.0	0.131
Parathyroid hormone	64.0	49.0	0.420
Albumin	45.2	64.9	0.649
Prealbumin	52.0	61.2	0.818
High sensitivity C-reactive protein	67.3	46.0	0.128
C-reactive protein, median	60.4	52.9	0.104
Tumor necrosis factor-alpha	63.6	50.9	0.354
Leptin	63.3	50.0	0.047

[a]No comparison analysis could be performed, because the factor variable has only one value for every stratum.

Table 3. Cox regression analysis for risk factors of poor survival

	B	Mean	SE	Wald	Sig.	Experience (B)	95% CI for Exp (B)	
							LB	UB
Age	0.526	0.643	0.333	2.489	0.115	0.591	0.307	1.136
Systolic BP	1.081	0.704	0.409	6.995	0.008	0.339	0.152	0.756
Diastolic BP	0.233	0.490	0.400	0.339	0.560	0.792	0.362	1.735
Kt/V	–0.217	0.357	0.313	0.481	0.488	1.242	0.673	2.292
Leptin	0.520	0.490	0.334	2.425	0.119	0.595	0.309	1.144
RIDWG	0.491	1.490	0.357	1.893	0.169	0.612	0.304	1.232

BP: Blood pressure; CI: Confidence interval; LB: Lower bound; UB: Upper bound; and RIDWG: Relative interdialytic weight gain.

Discussion

Our findings in a prospective cohort of maintenance hemodialysis patients revealed 5-year survival rate of 56.6% and association of younger age (<52 years), lower systolic (<120 mmHg) and diastolic (<80 mmHg) blood pressure, lower RIDWG (<4.7%), and Kt/V (≥1.6) values and lower serum leptin (<6.1 pg/mL) levels with better survival. The cox-regression analysis revealed that, among the factors associated with survival in the univariate analysis, only high SBP was a significant predictor of poor long-term survival in maintenance hemodialysis patients.

Identification of higher pre-dialysis SBP as the significant poor prognostic factor for long-term survival in the present cohort of maintenance hemodialysis patients seems notable given that hypertension was the most common etiology underlying CKD in our cohort. In fact, blood pressure control is the most established practice for preventing the progression and complications of CKD.[17] In a past study on long-term influence of blood pressure patterns on target organ damages, higher blood pressure burden (higher initial clinic SBP and pulse pressure) was reported to be associated with accelerated progression of estimated

glomerular filtration rate and worsening renal outcomes.[17] Our findings related to the poor prognostic impact of SBP on long-term survival support the findings from a past study among hemodialysis patients, which indicated the association of peridialytic SBP rise with higher mortality when combined with high pre-hemodialysis SBP, whereas with better survival when concurrent with low pre-hemodialysis SBP.[18]

Although not confirmed in multivariate analysis, younger patient age was associated with better survival in the univariate analysis in the present study. Similarly, in a past study, association of age with long-term survival was reported in maintenance hemodialysis patients and authors indicated younger patients to have a higher chance of being cured compared to the older ones.[4] The age was also reported among the predictors of survival in other studies about the survival of hemodialysis patients.[19-21]

Baseline levels for CRP were above the normal ranges in our study population, that elevated CRP was more common in malnourished dialysis patients.[22] In addition, baseline median serum albumin levels of 3.9 g/dL in our patients are notable given the robust correlations of serum albumin levels with mortality, hospitalization, and quality of life in both dialysis dependent and non-dialysis dependent CKD patients.[23]

Even though MIS has been considered a comprehensive scoring system with significant associations with prospective hospitalization and mortality and as a predictor of dialysis outcome, our findings revealed close to normal malnutrition-inflammation status (total MIS score of median 6, range 4–8), along with no significant impact of MIS as well as other measures of anemia, inflammation, and nutrition on survival in patients undergoing hemodialysis.[16] Our findings, in a cohort of patients who were on hemodialysis for median 54 months, seem notable in this regard given the high prevalence of protein-energy wasting reported in hemodialysis patients (range, 20–60%), as expected to increase further with duration of hemodialysis treatment.[24-27]

Nonetheless, although not confirmed in the cox-regression analysis, higher Kt/V (≥1.6), lower RIDWG (<4.7%), and lower serum leptin (<6.1 pg/mL) levels were also associated with better survival in the univariate analysis.

Hence, our findings support that the adequacy of dialysis, as measured by Kt/V, is an important prognostic factor in hemodialysis patients as associated with increased overall survival rate.[4,28,29] Likewise, increase in dialysis adequacy (Kt/V ≥1.2) was reported to increase the chance of being a long-term survivor in maintenance hemodialysis patients.[4]

In addition, better survival rates in our cohort with lower RIDWG (<4.7%) support the association of high RIDWG with increased risks for intradialytic hypotension, left ventricular hypertrophy, cardiovascular, and all-cause and mortality in hemodialysis patients.[29-34] In fact, increased risk of mortality and increased risk for fluid overload hospitalizations was reported for RIDWG ≥ 5.7% and RIDWG ≥ 4%, respectively, in hemodialysis patients.[30]

Our findings related to association of lower serum leptin levels (cut-off ≤6.1 pg/mL) with better survival in hemodialysis patients agree with consideration of leptin as a risk factor of all-cause mortality or CVD-related mortality.[36,37] Indeed, being a member of the middle-molecule toxins that cannot be removed by regular hemodialysis, leptin levels are significantly higher in patients with kidney failure than in the general population due to a reduced renal clearance.[11]

However, there is a controversy regarding the prognostic value of serum leptin levels in hemodialysis patients, possibly due to differences in the genetic background of studied populations.[11] In contrast to our findings, the relationship between low serum leptin concentration and increased mortality was reported in hemodialysis patients.[38] Likewise, in a past study among 53 hemodialysis patients, leptin levels less than the median (3.45 ng/mL) were reported to be associated with a shorter survival.[11] Authors also noted that leptin may not be a full uremic toxin given that hemodialysis patients with higher leptin levels survived significantly longer and concluded the association of a low serum leptin concentration with all-cause mortality, but not CVD mortality, in stable hemodialysis patients.[11] In addition, there are also studies reported no significant relationship between serum leptin levels and all-cause mortality in hemodialysis patients.[39]

In fact, hyperleptinemia is closely related to fat mass in chronic hemodialysis patients, and thus, patients with PEW were reported to have high leptin and high CRP levels, and higher mortality rate compared to the control group.[40] However, others reported that an inverse association of leptin with CRP levels and MIS scores, indicating the positive effects of leptin on nutrition which supports the theory of protective effects of leptin in hemodialysis patients.[41]

Nonetheless, it should be noted that the association serum leptin levels with survival was not confirmed in the current cox-regression analysis, and leptin levels have been suggested to reflect fat mass depots, rather than independently contributing to uremic anorexia, or modifying nutritional status and/or survival in chronic hemodialysis patients.[39]

There are several limitations in the study. First, due to single center design, generalizing our findings to overall hemodialysis population seems not possible. Second, relatively low sample size might prevent us to achieve the statistical

significance concerning the impact of certain parameters on survival. Third, lack of data on association of longitudinal changes in inflammatory and nutritional serum markers with mortality as well as lack of specific analysis of all-cause and cardiovascular mortality are other limitations which otherwise would extend the knowledge achieved in the present study. Nonetheless, providing data on potential prognostic factors through 5-year analysis, our findings represent a valuable contribution to the literature regarding long-term survival in maintenance hemodialysis patients.

Conclusion

In conclusion, our findings revealed that pre-dialysis SBP was the significant predictor of long-term survival in stable maintenance hemodialysis patients. Although not confirmed in the multivariate analysis, younger patient age, adequacy of dialysis, lower RIDWG, and lower serum leptin levels were associated with better survival in the univariate analysis, whereas MIS as well as other measures of anemia, inflammation, and nutrition had no significant impact on long-term survival. Future large-scale studies addressing the longitudinal changes in inflammatory and nutritional markers in relation to survivorship status are needed to better elucidate the prognostic factors for survival among maintenance hemodialysis patients.

Disclosures

Ethics Committee Approval: The study was conducted in accordance with the ethical principles stated in the "Declaration of Helsinki" and approved by the Sisli Etfal Training and Research Hospital Ethical Committee (on October 9, 2012 with number of 199) along with the permission for the use of patient data for publication purposes.

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Authorship Contributions: Concept – E.A.; Design – E.A.; Supervision – N.B.H.; Materials – E.A.; Data collection &/or processing – T.S.; Analysis and/or interpretation – M.S.; Literature search – T.B.; Critical review – A.U.

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