Original Article
Yonsei Med J 2021 Apr;62(4):315-324
https://doi.org/10.3349/ymj.2021.62.4.315
Yonsei Medical Journal
YMJ
pISSN: 0513-5796 · eISSN: 1976-2437

Different Seasonal Variations of Potassium in Hemodialysis Patients with High Longitudinal Potassium Levels: A Multicenter Cohort Study Using DialysisNet

Yunmi Kim[1]*, Seong Han Yun[2]*, Hoseok Koo[3], Subin Hwang[3], Hyo Jin Kim[4], Sunhwa Lee[5], Hyunjeong Baek[5], Hye Hyeon Kim[6], Kye Hwa Lee[6], Ju Han Kim[6], Ji In Park[5], and Kyung Don Yoo[7]

[1]Department of Internal Medicine, Inje University Busan Paik Hospital, Busan;
[2]Department of Nephrology, Changwon Fatima Hospital, Changwon;
[3]Department of Internal Medicine, Seoul Paik Hospital, Inje University College of Medicine, Seoul;
[4]Department of Internal Medicine, Pusan National University Hospital, Busan;
[5]Department of Medicine, Kangwon National University Hospital, Kangwon National University School of Medicine, Chuncheon;
[6]Department of Biomedical Informatics (SNUBI), Division of Biomedical Informatics, Seoul National University College of Medicine, Seoul;
[7]Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea.

Purpose: To determine seasonal variations in serum potassium levels among hemodialysis patients.
Materials and Methods: This was a multicenter cohort study of patients whounderwent hemodialysis and were registered in DialysisNet at our four associated general hospitals between January and December 2016. Month-to-month potassium variability was quantified as SD/√{n/(n-1)}, and a non-hierarchical method was used to cluster groups according to potassium trajectories. Seasonal variations in potassium levels were analyzed using a cosinor analysis.
Results: The analysis was performed on 279 patients with a mean potassium level of 5.08±0.58 mmol/L. After clustering, 52.3% (n=146) of patients were included in the moderate group (K^+, 4.6±0.4 mmol/L) and 47.7% (n=133) in the high group (K^+, 5.6±0.4 mmol/L). The mean potassium level peaked in January in the moderate group (4.83±0.74 mmol/L) and in August in the high group (5.51±0.70 mmol/L). In the high potassium group, potassium levels were significantly higher in summer than in autumn (p<0.001) and spring (p=0.007). Month-to-month potassium variability was greater in the high group than in the moderate group (0.59±0.19 mmol/L vs. 0.52±0.21 mmol/L, respectively, p=0.012). Compared to patients in the first quartile of potassium variability (≤0.395 mmol/L), those with higher variability (2nd–4th quartiles) were 2.8–4.2 fold more likely to be in the high potassium group.
Conclusion: Different seasonal patterns of serum potassium were identified in the moderate and high potassium groups, with potassium levels being significantly higher in the summer season in the high potassium group and in winter for the moderate potassium group.

Key Words: End-stage renal disease, hemodialysis, potassium, seasonal variation

Received: July 21, 2020 **Revised:** January 4, 2021 **Accepted:** January 11, 2021
Co-corresponding authors: Kyung Don Yoo, MD, PhD, Division of Nephrology, Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, 877 Bangeojinsunhwan-doro, Dong-gu, Ulsan 44033, Korea.
Tel: 82-52-250-8656, Fax: 82-52-250-8075, E-mail: ykd9062@gmail.com and
Ji In Park, MD, Department of Medicine, Kangwon National University Hospital, Kangwon National University School of Medicine, 1 Gangwondaehak-gil, Chuncheon 24289, Korea.
Tel: 82-33-258-9204, Fax: 82-33-258-2404, E-mail: park.jiin@gmail.com

*Yunmi Kim and Seong Han Yun contributed equally to this work.

INTRODUCTION

Potassium plays a vital role in maintaining a stable cellular membrane potential and triggering action potentials in the nerves, muscles, and heart. Ingested potassium is excreted via metabolic pathways, with >90% of potassium being excreted by the kidneys.[1] Excessive potassium intake, metabolic acidosis, inadequate dialysis efficacy, such as low Kt/V, renin-angiotensin-aldosterone system blockade, and frequent transfusions may lead to increased serum potassium levels in patients with end-stage renal disease (ESRD) requiring renal replacement therapy.[1] Hyperkalemia, a condition in which potassium levels are higher than normal, is associated with increased arrhythmia-related mortality in patients undergoing maintenance hemodialysis.[2]

A study involving 36888 patients undergoing hemodialysis in the United States between 2007 and 2010 reported a prevalence of hyperkalemia of 16 per 100 patient-months. Moreover, the mortality rate was seen to increase significantly when the potassium level was ≥5.7 mmol/L.[2] Although the extent to which potassium levels can be controlled is an important prognostic factor, achieving such control is difficult. In the multinational Dialysis Outcome Practice Pattern Study, 6.2–20.0% of patients undergoing hemodialysis had a potassium level ≥6.0 mmol/L.[3] In the Clinical Research Center for End-Stage Renal Disease cohort study, which included 3230 patients with ESRD in South Korea, the mean potassium level was 4.9±0.7 mmol/L, with a potassium level >5.0 mmol/L identified in 36% of patients.[4] However, these studies did not consider longitudinal potassium levels using serial measurements.

Hemodialysis alone is insufficient for maintaining normokalemia, and dietary control plays a crucial role in achieving stable potassium levels.[5] Yet, only few studies have addressed this issue. Moreover, it is known that in patients on hemodialysis, compliance with dietary and water restriction is as low as 25–86%.[6] Although many medical institutions have implemented dietary education for patients on hemodialysis, this education has not consistently translated to improved compliance with dietary restrictions.[7] Seasonal variation in dietary habits is a specific cause of changes in potassium level among patients on hemodialysis.[8,9]

In the participating hospitals, we used the Health Avatar Platform-based DialysisNet (DNet)[10] to improve the management of patients undergoing hemodialysis. This system allows early detection of hyperkalemia and identification of overall trends. Therefore, the purpose of our study was to identify differences in potassium levels between patients with moderate and high longitudinal potassium trajectories and to determine seasonal differences between these two groups using DNet.

MATERIALS AND METHODS

Statement of ethics

This study was approved by the Institutional Review Boards of Seoul Paik Hospital (IIT-2016-216), Dongguk University Gyeongju Hospital (110757-201608-HR-06-01), Kangwon National University Hospital (KNUH-2016-08-006), and Changwon Fatima Hospital (CFH-2018-18-02). The requirement for patient informed consent was waived owing to the retrospective nature of the study. All clinical investigations were conducted in accordance with the principles of the Declaration of Helsinki.

Compliance method with standard models and development of a multicenter trial concept in DialysisNet

DNet is an smartpad-based, integrated, clinical information system for nephrologists in dialysis units. DNet displays test results, including potassium levels, in real-time and determines whether the results are normal or abnormal. For the effective management of hemodialysis data, we identified common data elements of hemodialysis information (CDEHI) and utilized these in DNet. We used the American Society for Testing and Materials (ASTM) Continuity of Care Record (CCR) and ISO/IEC 11179 to evaluate compliance with a standard model for CDEHI. The ASTM CCR is the standard model for the expression and transfer of health record summaries.[10] The ISO/IEC 11179 Metadata Registry standard describes a method for standardizing and registering data elements to make them understandable and shareable between studies and institutions. ISO/IEC 11179 was used to represent common data as metadata, with these data verified using the ASTM CCR/Extensible Markup Language (XML) schema definition before being parsed into the database. Subsequently, the metadata were stored in the Health Avatar Platform using the representational state transfer protocol.[11] The DNet common data model, for which we used the CDEHI, was selected after a syntactic and semantic interoperability review and developed by a consortium of DNet user groups. The CDEHI transforms observational data, both administrative and clinical, standardizing the content and format for use in common queries.

Study population

Four general hospitals in Korea participated in this retrospective study: Inje University Seoul Paik Hospital, Dongguk University Gyeongju Hospital, Kangwon National University Hospital, and Changwon Fatima Hospital. The study included patients ≥18 years of age who underwent maintenance hemodialysis two times per week or more, and had completed eight hemodialysis sessions per month or more for over 3 months between January and December 2016.

https://doi.org/10.3349/ymj.2021.62.4.315

Clinical data collection and laboratory evaluations

Data related to hyperkalemia were analyzed, of which values closest to the first day of each month were automatically selected. Data were extracted from the common data model of DNet, as per previously described methods.[12] The variables collected and analyzed for this study were as follows: serum potassium, potassium test date, hemoglobin, hematocrit, iron, total iron-binding capacity (TIBC), Kt/V, aspartate aminotransferase, alanine aminotransferase, and prescription of angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB). Transferrin saturation was calculated as 100×serum iron/TIBC (%). The dialysis unit in all four participating hospitals had been accredited by the Korean Society of Nephrology during the study period,[13] which requires laboratory tests to be obtained and recorded according to predetermined standards. Finally, we collected data on all-cause deaths until August 2019. All data were encrypted and sent to BioEMR for analysis.

Development of the BioEMR for multicenter trials in DialysisNet

The BioEMR provides clinical and bioinformation, and is equipped for sharing technology.[14] BioEMR includes the following features: an extractor that converts hospital information and clinical genetic information into XML; an integrated development environment (IDE), which is a repository of XML; an integrated analysis for IDE data; a case report form; conversion of the common data elements to a clinico-histopathological metadata registry (CHMR); and verification of terminology. For our study, we created metadata and operate/reposit forms using standard terminology. Clinical documents were also received in XML format, and they were stored in the clinical results database after metadata validation. Within the electronic medical record system of each hospital, order communication system data were converted using the CCR standard,[15] and laboratory information were converted using the Logical Observation Identifiers Names and Codes (LOINC®) standard.[16] After XML representation was performed, using the BioEMR extractor, the data were stored in CHMR format, and metadata-validation enhancement data indexing were gathered into the research data.

Operational definitions in this study

Cluster analysis was performed using monthly trajectories of observed potassium values. Patients were categorized into two groups based on K-means clustering for the potassium trajectory between the groups; these two groups were defined as the moderate and high potassium groups. The analysis included the potassium values of patients who underwent blood chemistry evaluation including potassium testing, at least once per month and had ≥eight monthly potassium values for 1 year during the study period. Among the 279 patients included in our study, 242 had potassium levels evaluated once a month for 12 months, 16 had monthly potassium levels evaluated for 11 months, 12 had potassium levels evaluated for 10 months, seven had potassium levels evaluated for 9 months, and two had potassium levels evaluated for 8 months. Month-to-month changes in average potassium values were calculated for each patient [mean±standard deviation (SD)], as previously described.[12] The within-subject SDs for serially measured potassium values were adjusted for the number of assessments (n) for each patient.[12] The month-to-month variability of potassium was calculated as the within-subject SD/√{n/(n-1)}.[17] For our analysis, the seasons were defined as follows: winter from December to February, spring from March to May, summer from June to August, and autumn from September to November.

Statistical analyses

Analyses were performed using R (version 3.5.3., R Foundation for Statistical Computing, Vienna, Austria) and SPSS ver 24.0 (IBM Corp., Armonk, NY, USA). Continuous variables were reported as mean±SD, and categorical variables were reported as frequencies and percentages. For continuous variables, Student's t-test and analysis of variance were performed to determine intergroup differences as appropriate. Chi-squared test was used to determine the nature of associations between categorical variables. K-means were used for clustering of patients, based on each individual's potassium trajectories, using a non-hierarchical method which uses an algorithm that binds given data into k-clusters. We also used an unsupervised machine learning algorithm that provides a method for minimizing the variance between each cluster and distance.[18,19] We used the kml and kml3d packages in R for cluster analyses, providing an implementation of k-means.[19] For the clustering evaluation scale, all three categories were used for internal evaluation,[20] including the Calinski–Harabatz index,[21] Ray–Tuni,[22] and Davies–Bouldin index[23] for concordant criteria (Fig. 1). The function plotAllCriterion( ), using the kml and kml3d packages in R, displayed several criteria on the same graph.[19] We also allocated patients into four groups based on the quartile of the variability in potassium levels for sensitivity analysis. Logistic regression analysis was performed to identify factors associated with the high potassium trajectory group. Age, sex, and variables that were significant in univariate analysis were selected for multivariate-adjusted analysis. We conducted the paired t-test to examine differences in potassium levels between adjacent seasons in each potassium group using repeated measurements of potassium levels of each individual. We conducted Kaplan-Meier survival analysis for all-cause death events. Patients' survival was followed from the start of this study to August 2019. The patients were censored before the end of follow-up in case of transfer to other medical center, kidney transplantation, modality change to peritoneal dialysis, or loss to follow-up. Intergroup differences were determined using log-rank test. p-values <0.05 were considered statistically

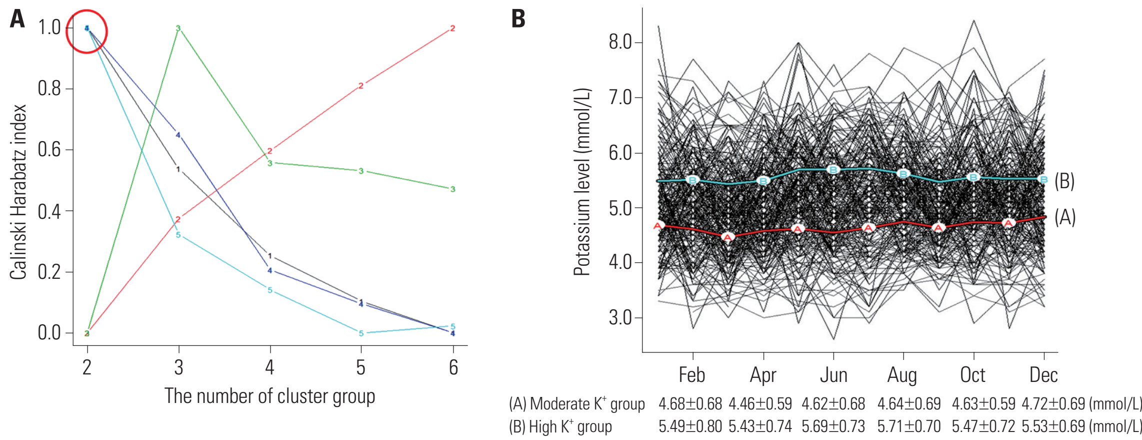

Fig. 1. Group clustering according to serum potassium trajectories. (A) Comparison of internal validation of clustering analysis by concordant criteria. The line numbers 1, 2, 3 are Calinski Harabatz index, 4 is RayTuni index, and 5 is Davies Bouldin index. Concordant criteria showed agreement on two group clustering (red circle). (B) The difference in potassium levels between groups along with the seasons.

significant.

We analyzed the amplitude and acrophase of serum potassium levels between the groups after clustering using cosinor analysis.[24-26] This is a statistical method that returns time-series data to the cosine function. The analysis approximates the following equation to minimize the root mean square error:[26]

$$Y(t)=Mesor+A\cos(2\pi t/\tau+\varphi)+e(t),$$

where Y(t) is data collected at times ti (i=1, ..., N); Mesor is the midline estimating statistic of rhythm, A is the amplitude, a measure of the extent of predictable changes above and below the midline within a cycle; φ is the acrophase, a measure of the timing of overall high values; τ is the period, defined as the duration of one cycle (in this study, the cycle rhythm was 12 months); and e(t) is the error term at each time. To fit the periodic model, the outcome of interest Y, at time variable t, for a fixed period D, was calculated as follows:

$$Y(t)=intercept+amplitude*\cos(2\pi t/D-acrophase)+\varepsilon$$

The amplitude was calculated as $A=\sqrt{(c^2+s^2)}$, (A≥0), and the phase (in radians) as P={arctan (s/c), c≥0; arctan (s/c)+π, c<0, s≥0; arctan (s/c)-π, c<0, s>0}. $c=\frac{1}{n}\sum_{n-1}^{n}\cos(wt)$, $s=\frac{1}{n}\sum_{n-1}^{n}\sin(Wt)$, t=1, ... , n, wt=2πft. P (estimated phase)=12 (P/2π)+1 is shown in Fig. 2.

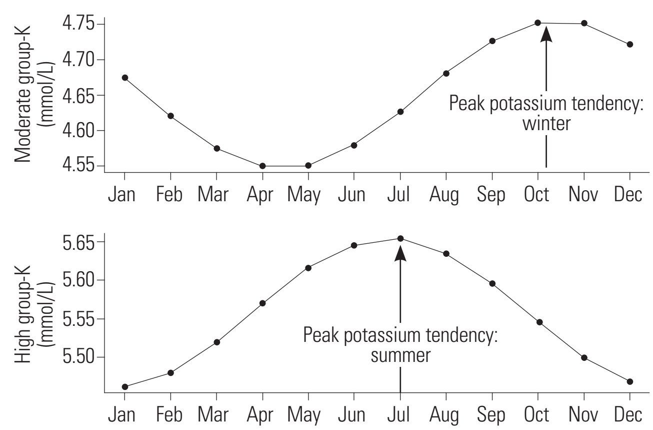

Fig. 2. Cosinor analysis for the variation of serum potassium level. The seasonal pattern at which the peak of a rhythm occurred (acrophase) was from June to August in the high potassium group, whereas the acrophase occurred from September to December in the moderate potassium group.

RESULTS

Demographic and clinical characteristics

Trajectory analysis showed that 52.3% (n=146) of patients were included in the moderate potassium group and 47.7% (n=133) in the high potassium group (Fig. 1). The mean patient age was 63.3±13.1 years, with 55.9% of patients being men, 58.4% having diabetes mellitus, and 83.8% having hypertension. The baseline clinical and laboratory characteristics, according to potassium clustering groups, are reported in Table 1. While the Kt/V and proportion of patients who were taking ACEi or ARB were comparable between the moderate and high groups, patients in the high group had a longer duration of dialysis (48.2±40.6 months vs. 72.4±63.2 months, respectively, *p*<0.001) and were younger (65.2±13.4 years vs. 61.3±12.5 years, respectively, *p*=0.013) compared to the moderate group. The baseline phosphorus level was higher in the high potassium group than in the moderate potassium group (5.2±1.6 months vs. 4.5±1.5 months, respectively, *p*=0.001). The mean initial potassium level was 4.7±1.5 mmol/L in total patients, 4.2±1.6 mmol/L in the moderate group, and 5.3±1.2 mmol/L in the high group (*p*<0.001) (Table 1). The proportion of patients with hyperkalemia (potassium values >5.5 mmol/L) was significantly higher in the high group for each month (Supplementary Table 1, only online).

Of the 279 patients included in the analysis, 35 were from

https://doi.org/10.3349/ymj.2021.62.4.315

Table 1. Baseline Characteristics of the Study Subjects according to Potassium Groups

Characteristics	Total (n=279)	K+ clustering group		
		Moderate (n=146)	High (n=133)	*p* value
Age	63.3±13.1	65.2±13.4	61.3±12.5	0.013
Sex, male	156 (55.9)	74 (50.7)	82 (61.7)	0.065
BMI (kg/m^2)	23.3±3.3	22.4±3.4	22.4±3.3	0.936
DM	163 (58.4)	85 (58.2)	78 (58.6)	0.942
Hypertension	234 (83.8)	124 (84.9)	110 (82.7)	0.614
Cause of ESRD				0.044
DM	155 (55.6)	80 (54.8)	75 (56.4)	
Hypertension	71 (25.8)	35 (24.0)	37 (27.8)	
CGN	16 (5.7)	8 (4.1)	10 (7.5)	
PKD	2 (0.7)	0 (0.0)	2 (1.5)	
Others	33 (11.8)	25 (17.1)	9 (6.8)	
Dialysis vintage (months)	59.4±53.8	48.2±40.6	72.4±63.2	<0.001
Kt/V	1.63±0.46	1.58±0.36	1.56±0.34	0.617
Hemoglobin (g/dL)	10.2±1.0	10.2±1.0	10.4±1.4	0.160
Hematocrit (%)	31.3±2.3	30.8±2.8	31.7±3.3	0.012
Iron (μg/dL)	64.9±19.6	65.7±28.5	69.9±33.3	0.262
TIBC (μg/dL)	229.7±35.7	227.5±39.6	227.3±39.3	0.960
TSAT (%)	30.1±13.3	29.2±12.4	31.2±14.2	0.208
Albumin (g/dL)	3.7±0.2	3.7±0.3	3.8±0.3	0.031
AST (U/L)	20.2±9.0	21.2±11.8	20.9±16.1	0.819
ALT (U/L)	16.8±7.5	17.9±12.6	16.3±7.4	0.214
ACEi or ARB, yes	162 (58.0)	80 (54.8)	82 (61.7)	0.246
K (mmol/L)	4.7±1.5	4.2±1.6	5.3±1.2	<0.001
Ca (mg/dL)	9.0±0.8	9.0±0.8	9.0±0.8	0.988
P (mg/dL)	4.8±1.6	4.5±1.5	5.2±1.6	0.001

BMI, body mass index; DM, diabetes mellitus; ESRD, end stage renal disease; CGN, chronic glomerulonephritis; PKD, polycystic kidney disease; TIBC, total iron-binding capacity; TSAT, transferrin saturation; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker.
Data are presented as mean±standard deviation or n (%).

hospital A, 21 from hospital B, 103 from hospital C, and 120 from hospital D (Supplementary Table 2, only online). The proportion of patients in the high potassium group was 40.0%, 61.9%, 49.1%, and 57.2% in A, B, C, and D hospitals, respectively. The Kt/V in the overall cohort was 1.63±0.46, with the highest value being from hospital C (1.75±0.59) and the lowest from hospital A (1.31±0.23). There were no significant differences among hospitals in terms of dialysis duration or hemoglobin concentrations.

Difference in serum potassium levels according to clustering groups by trajectory analysis and seasons

The overall mean potassium level over 12 months was 5.1±0.6 mmol/L in total patients, 4.7±0.4 mmol/L in the moderate group, and 5.6±0.4 mmol/L in the high group (p<0.001). January had the highest mean potassium level (4.83±0.74 mmol/L) and April had the lowest mean potassium level (4.46±0.59 mmol/L) in the moderate potassium group, whereas, for the high group, August had the highest (5.71±0.70 mmol/L) and April had the lowest (5.43±0.74 mmol/L) (Supplementary Fig. 1, only online). In the moderate potassium group, categorized by seasons, the mean potassium level was generally stable throughout the year, with levels being higher in winter than in spring (p=0.002). In the high potassium group, potassium levels were significantly higher in summer than autumn (p<0.001) and spring (p=0.007) (Fig. 3). This pattern was sustained when data extending over 2 years were analyzed (Supplementary Fig. 2, only online).

Cosinor analysis for potassium seasonal variation between clustering groups

The amplitude value is indicated by the difference in the mesor and peak values of the target variable and the acrophase value by the difference in time (namely month in this study) from the point of time when the peak value appears.[27] Given the time variable used (month) and optional covariates (clustering group according to potassium trajectory), inferences can be made regarding the fit of the cosinor function. A Wald test was used to compare covariates between the two groups.[27] The global test revealed differences in the path coefficients of amplitude (p<0.001) and acrophase (p=0.005) between the groups (Supplementary Table 3, only online). Between-group

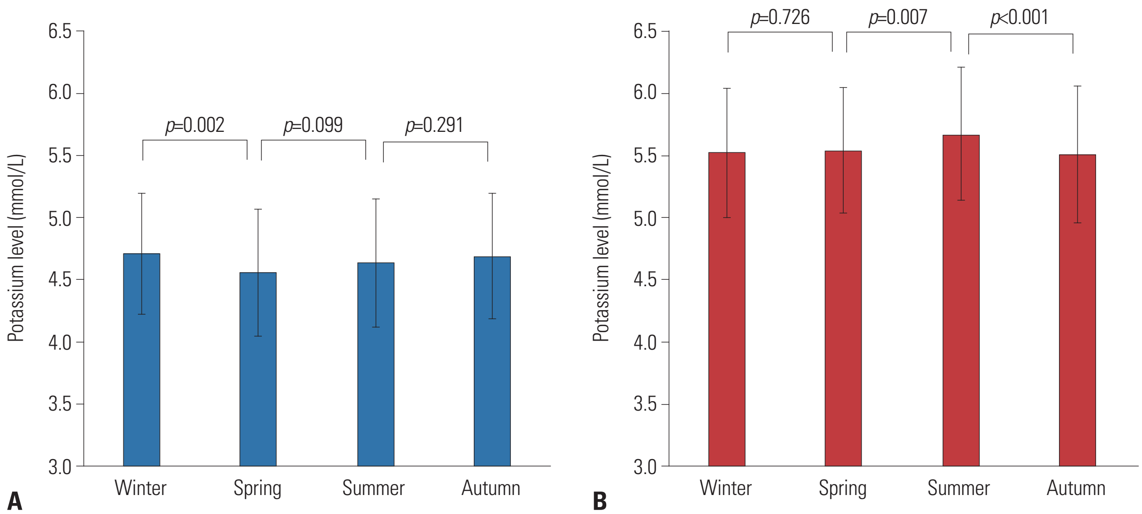

Fig. 3. Comparison of seasonal potassium levels by group. (A) Moderate group. (B) High group.

Table 2. Cosinor Analysis of Potassium Seasonal Variation between Groups

	Estimate	Standard error	95% CI	*p* value
High K^+ group (ref. moderate K^+ group)	0.906	0.024	0.859–0.954	<0.001
Amplitude: Moderate K^+ group (mg/dL)	0.104	0.023	0.005–0.150	<0.001
Amplitude: High K^+ group (mg/dL)	0.009	0.024	0.004–0.145	<0.001
Acrophase: Moderate K^+ group (month)	-0.814	0.228	-1.262–-0.367	<0.001
Acrophase: High K^+ group (month)	0.394	0.254	-0.104–0.892	0.121

CI, confidence interval; K^+, potassium.

differences in the cosinor fit analysis are shown in Table 2, with significant differences in amplitude and acrophase, by covariate values, between the two groups. Compared to the moderate potassium group, the potassium level of the high potassium group increased by 0.906 mmol/L [95% confidence interval (CI), 0.859–0.954, $p<0.001$]. The acrophases of potassium trajectories were different in the moderate and high potassium groups, indicative of different patterns of seasonal variation in serum potassium levels between the two groups (Fig. 2). The mesor in patients with moderate potassium levels was 4.64 mmol/L, compared to 5.58 mmol/L for the high potassium level group.

Association of longitudinal high potassium group with month-to-month potassium variability and mortality

The high potassium group showed higher month-to-month potassium variability compared to the moderate potassium group (0.59±0.19 mmol/L vs. 0.52±0.21 mmol/L, $p=0.012$). Compared to patients in the 1st quartile of potassium variability (≤0.395 mmol/L), those with higher potassium variability (2nd to 4th quartiles) were 2.8–4.2 times more likely to belong to the high potassium group (Table 3).

Finally, to determine the influence of serum potassium levels on outcomes in a sensitivity analysis, we collected data of all-cause death events up to August 2019. Of the 279 patients included, 42 deaths occurred over a median follow-up of 43 months [interquartile range (IQR), 27–43 months]. There was no significant difference in cumulative survival between the moderate and high potassium level groups (Log-rank, $p=0.236$) (Fig. 4A). However, higher month-to-month potassium variability was associated with long-term mortality, irrespective of the potassium group (Fig. 4B).

DISCUSSION

In this study, we investigated the pattern of potassium levels among hemodialysis patients, using trajectory analysis to classify patients as having a moderate or high potassium level. The seasonal variation in potassium levels was different between the two groups. In the moderate group, potassium levels were highest in the winter, while in the high group, potassium levels were highest in the summer. Several studies have previously reported a seasonal variation in potassium levels among hemodialysis patients.[28-30] To the best of our knowledge, this is the first study which attempted to classify patients into groups according to the longitudinal potassium levels, revealing a difference in the pattern of seasonal potassium variability between the groups.

Seasonal variations in potassium levels have been investi-

https://doi.org/10.3349/ymj.2021.62.4.315

Table 3. Variables Associated with the High Potassium Group by Logistic Regression Analysis

Variables	Unadjusted OR (95% CI)	*p* value	Adjusted OR* (95% CI)	*p* value
Age (per 1 year)	0.977 (0.959–0.995)	0.014	0.964 (0.941–0.988)	0.003
Sex (male vs. female)	1.564 (0.971–2.520)	0.066	1.730 (1.002–2.986)	0.049
DM (yes vs. no)	1.018 (0.632–1.639)	0.942		
Hypertension (yes vs. no)	0.849 (0.448–1.607)	0.614		
BMI (per 1 kg/m^2)	0.997 (0.929–1.070)	0.936		
Dialysis vintage (per 1 month)	1.010 (1.004–1.015)	<0.001	1.010 (1.004–1.016)	0.001
Single-pool Kt/V (per 1)	0.799 (0.334–1.913)	0.799		
Hemoglobin (per 1 g/dL)	1.154 (0.949–1.408)	0.158		
Albumin (per 1 g/dL)	2.335 (1.068–5.106)	0.034	1.822 (0.709–4.557)	0.200
ACEi or ARB (yes vs. no)	1.326 (0.823–2.139)	0.247		
Mean Na^+ (per 1 mmol/L)	1.014 (0.926–1.110)	0.770		
K^+ variability†				
1st quartile, ≤0.395	Reference		Reference	
2nd quartile, 0.396–0.532	2.286 (1.141–4.578)	0.020	2.825 (1.289–6.195)	0.010
3rd quartile, 0.533–0.686	3.232 (1.606–6.503)	0.001	5.115 (2.271–11.521)	<0.001
4th quartile, >0.687	2.420 (1.208–4.848)	0.013	4.248 (1.827–9.878)	0.001

DM, diabetes mellitus; BMI, body mass index; ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval; OR, odds ratio.
*Adjusted for age, sex, dialysis vintage, albumin, and K^+ variability, †K^+ variability was defined as standard deviation of [K^+ (mmol/L)]/{√[n/(n–1)]}.

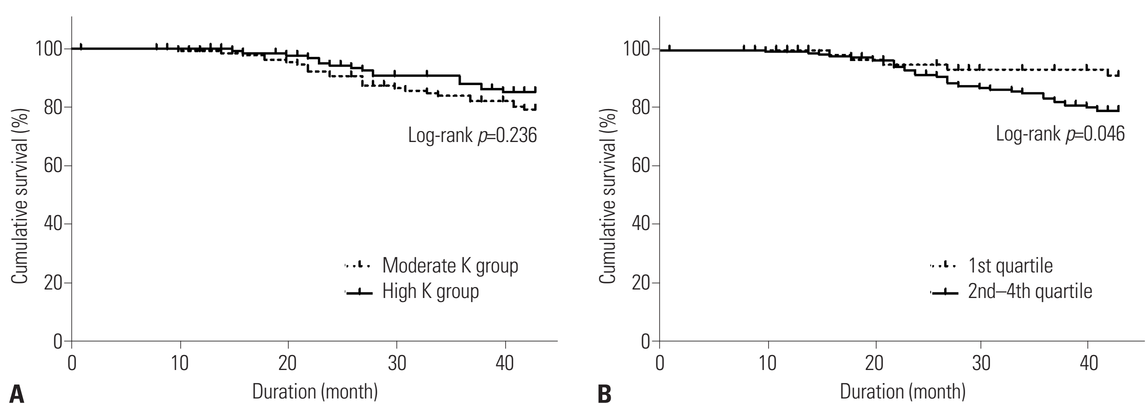

Fig. 4. Survival analysis for the longitudinal potassium level. (A) Kaplan-Meier analysis for survival according to K^+ clustering group. (B) Kaplan-Meier analysis for survival according to K^+ variability.

gated in several cohorts. In 2002, Cheung, et al.[29] reported several clinical and laboratory variables for hemodialysis patients on a monthly basis, with a peak in potassium levels in the winter, more specifically in February. In 2008, one Japanese study reported a peak in potassium levels in December and a trough in June.[28] The most recent and largest cohort study, including 15056 hemodialysis patients, reported seasonal variations in potassium levels, with the highest values in the winter and lowest values in the summer.[30] As seasons are different between the two hemispheres, these three previous studies were conducted in the United States and Japan, both of which are in the northern hemisphere and at similar latitudes; therefore, it is not surprising that they all reported peaks in the winter. Previous studies have suggested that the peak potassium level in the winter is related to a higher total dietary intake during this season.[31] Another possible contributing factor is the substantial amount of potassium that is excreted with sweating during the summer. Indeed, potassium levels in sweat have previously been reported to be significantly higher in patients with renal failure than in healthy controls.[32]

However, contrary to the findings of previous studies, nephrologists commonly see patients presenting with fatal hyperkalemia in the summer due to a large intake of seasonal fruits and vegetables. Several studies have reported significant changes in fresh vegetable and fruit intake over the seasons, with double the intake being reported in summer and autumn compared to winter.[33,34] A mini-review also revealed that in patients with chronic kidney disease, hyperkalemia is most commonly caused by the intake of fruits and vegetables.[35] In the present study, we characterized seasonal variations in potassium levels using a between-group cosinor analysis, with patients classified based on their potassium trajectories into the moderate and high potassium level groups. Only the moderate potassium group showed a seasonal variation in potassium levels that was consistent with that seen in previous reports, with the highest potassium levels reported in the winter. In contrast, the high potassium group demonstrated interesting and novel findings, with higher mean potassium levels than in the moderate group throughout the year, as well as a peak in potassium level in the summer (Fig. 2). This suggests that cases with fatal hyperkalemia may present more frequently in the summer, despite a peak in the mean potassium values among dialysis patients in other seasons. Evaluation of the clinical values of patients in the high potassium level group indicated that they were younger and had undergone hemodialysis for longer durations compared to patients in the moderate potassium group. In previous studies, younger age has been reported to be the most important demographic correlate of behavioral nonadherence to treatment, including skipping dialysis sessions or not following a restricted diet.[36,37] Longer duration of hemodialysis has also been related to lower residual renal function,[38] which is a risk factor for hyperkalemia due to lower excretion of potassium from the kidneys. Based on our results, we suggest that younger patients with longer dialysis durations showing relatively high potassium levels throughout the year should be warned and closely monitored for hyperkalemia, especially in summer.

The high potassium group demonstrated higher variability in potassium levels. Although the mortality rate was not different between the two groups, variability in potassium levels was significantly related to mortality. A higher mean potassium level may not only be indicative of poorer diet compliance but may also be indicative of better nutrition.[39] Supporting this notion is the observation that, in the high group, the mean levels of serum albumin and phosphorus were higher than those of the moderate group. This may explain the comparable rate of all-cause mortality between the two groups. Further studies with longer follow-up durations, investigating the cause of death, particularly those related to hyperkalemia, are warranted.

One of the strengths of our research was the analysis of multicenter data collected using DNet. Since DNet accumulates real-time data at several dialysis centers using a common data model, it eliminates the enormous effort required to collect data on numerous variables from various electronic medical records at several centers. The risk of human error was minimal since data are sent to the DNet server automatically from hospital records (Supplementary Fig. 3, only online). This tool shows promise for dealing with repetitively measured data from patients on hemodialysis. In addition, DNet is connected to another platform, Avatar Beans, a smartphone application that updates patients on their laboratory test results and allows them to access these results, including monthly graphs, at any time (Supplementary Fig. 4, only online). It has recently been reported that using smartphone applications changes individual behavior in ways that enhance self-management ability in patients with advanced chronic kidney disease.[40] In a future study, we plan to intervene in patient self-management using the Avatar Beans application connected to DNet.

The current study had several limitations. First, the period of observation for some patients could have been as short as 1 year. We compared the potassium levels of these patients between seasons during the extended period of 2016–2017; this has been presented as Supplementary Fig. 2 (only online). The overall pattern was similar to the 1-year data analysis. A longer observation period is likely to provide more reliable results. Second, there was a lack of data on hospitalization or mortality related to hyperkalemia. We also collected data on all-cause death events until August 2019 (Fig. 4); a detailed analysis of the cause of death is warranted. Third, data regarding dietary records, medication including potassium binders, and residual renal function were not included in our analysis; therefore, the extent of analysis of factors that contributed to the seasonal variation of potassium level was not sufficient. Future studies investigating these factors and outcomes are needed to validate our findings.

In conclusion, we categorized patients undergoing hemodialysis into two groups according to their longitudinal potassium levels, and showed that the two groups exhibited different seasonal variation patterns. In general, potassium levels are higher in the winter in patients undergoing hemodialysis; however, in this study, the group defined as having high potassium levels showed higher year-round mean potassium levels, with peak levels observed in the summer. These findings may provide important evidence supporting the individualized management of patients undergoing hemodialysis.

ACKNOWLEDGEMENTS

We express our sincere gratitude to all of the medical centers using DialysisNet (DNet). The following nine hospitals have signed an MOU agreement with SNUBI and are utilizing DNet: Korea University Guro Hospital, Inje University Seoul Baik Hospital, Kangwon National University Hospital, Korea University Ansan Hospital, Dongguk University Gyeongju Hospital, Busan National University Hospital, Konyang University Hospital, Chungbuk National University Hospital , and Daejeon Eulji Medical Center.

Without an MOU agreement, the following hospitals have also been operating DNet: Changwon Fatima Hospital, Kwak Medical Clinic, Chung-ang University Hospital, Myung Ji hospital, Kyungpook National University Chilgok Hospital. Moreover, there are hospitals that are preparing to use DNet, including Hallym University Hangang Sacred Heart Hospital, Hallym University Kangnam Sacred Heart Hospital, Shihwa Medical Center, SMG Yonsei Hospital, Chonbuk National University Hospital, and Chonnam National University Hospital.

AUTHOR CONTRIBUTIONS

Conceptualization: Hoseok Koo, Kyung Don Yoo, and Ji In Park. Data curation: Subin Hwang, Hyo Jin Kim, Sunhwa Lee, and Hyunjeong Baek. Formal analysis: Hoseok Koo and Kyung Don Yoo. Investigation: Yunmi Kim and Seong Han Yun. Methodology: Hoseok Koo and Hye Hyeon Kim. Project administration: Hye Hyeon Kim and Kye Hwa Lee. Resources: Hye Hyeon Kim, Kye Hwa Lee, and Ju Han Kim. Software: Hye Hyeon Kim and Kye Hwa Lee. Supervision: Ju Han Kim. Validation: Ji In Park and Ju Han Kim. Visualization: Hoseok Koo and Hye Hyeon Kim. Writing—original draft: Yunmi Kim and Seong Han Yun. Writing—review & editing: Hoseok Koo, Kyung Don Yoo, and Ji In Park. Approval of final manuscript: all authors.

ORCID iDs

Yunmi Kim	https://orcid.org/0000-0001-9281-9926
Seong Han Yun	https://orcid.org/0000-0002-6221-3824
Hoseok Koo	https://orcid.org/0000-0001-7856-8083
Subin Hwang	https://orcid.org/0000-0001-6694-0861
Hyo Jin Kim	https://orcid.org/0000-0001-9289-9073
Sunhwa Lee	https://orcid.org/0000-0002-2883-3499
Hyunjeong Baek	https://orcid.org/0000-0003-1325-3392
Hye Hyeon Kim	https://orcid.org/0000-0002-1928-4168
Kye Hwa Lee	https://orcid.org/0000-0002-7593-7020
Ju Han Kim	https://orcid.org/0000-0003-1522-9038
Ji In Park	https://orcid.org/0000-0003-4662-3759
Kyung Don Yoo	https://orcid.org/0000-0001-6545-6517

REFERENCES

1. DuBose TD Jr. Regulation of potassium homeostasis in CKD. Adv Chronic Kidney Dis 2017;24:305-14.
2. Yusuf AA, Hu Y, Singh B, Menoyo JA, Wetmore JB. Serum potassium levels and mortality in hemodialysis patients: a retrospective cohort study. Am J Nephrol 2016;44:179-86.
3. Saran R, Bragg-Gresham JL, Rayner HC, Goodkin DA, Keen ML, Van Dijk PC, et al. Nonadherence in hemodialysis: associations with mortality, hospitalization, and practice patterns in the DOPPS. Kidney Int 2003;64:254-62.
4. Lee S, Kang E, Yoo KD, Choi Y, Kim DK, Joo KW, et al. Lower serum potassium associated with increased mortality in dialysis patients: a nationwide prospective observational cohort study in Korea. PLoS One 2017;12:e0171842.
5. Palmer SC, Ruospo M, Campbell KL, Garcia Larsen V, Saglimbene V, Natale P, et al. Nutrition and dietary intake and their association with mortality and hospitalisation in adults with chronic kidney disease treated with haemodialysis: protocol for DIET-HD, a prospective multinational cohort study. BMJ Open 2015;5:e006897.
6. Bame SI, Petersen N, Wray NP. Variation in hemodialysis patient compliance according to demographic characteristics. Soc Sci Med 1993;37:1035-43.
7. Durose CL, Holdsworth M, Watson V, Przygrodzka F. Knowledge of dietary restrictions and the medical consequences of noncompliance by patients on hemodialysis are not predictive of dietary compliance. J Am Diet Assoc 2004;104:35-41.
8. Cox BD, Whichelow MJ, Prevost AT. Seasonal consumption of salad vegetables and fresh fruit in relation to the development of cardiovascular disease and cancer. Public Health Nutr 2000;3:19-29.
9. Kovacic V, Kovacic V. Seasonal variations of clinical and biochemical parameters in chronic haemodialysis. Ann Acad Med Singap 2004;33:763-8.
10. Kim JH. Health avatar: an informatics platform for personal and private big data. Healthc Inform Res 2014;20:1-2.
11. Ku HS, Kim S, Kim H, Chung HJ, Park YR, Kim JH. DialysisNet: application for integrating and management data sources of hemodialysis information by continuity of care record. Healthc Inform Res 2014;20:145-51.
12. Kim HJ, Park JI, Yoo KD, Kim Y, Baek H, Kim SH, et al. Real-world treatment patterns of renal anemia in hemodialysis patients: a multicenter cohort study performed using DialysisNet (RRAHD study). Medicine (Baltimore) 2020;99:e18749.
13. Lee YK, Kim K, Kim DJ. Current status and standards for establishment of hemodialysis units in Korea. Korean J Intern Med 2013; 28:274-84.
14. Park YR, Bae YJ, Kim JH. BioEMR: an integrative framework for cancer research with multiple genomic technologies. Summit Transl Bioinform 2008;2008:81-4.
15. Health Level Seven International. HL7 Standards-Section 1: Primary standards. Health Level Seven International (HL7) [Internet]. [accessed on 2019 Dec 27]. Available at: http://www.hl7.org/implement/standards/product_section.cfm?section=1.
16. Huser V. Evaluation of LOINC as a reference terminology for clinical document types: A case report of an outpatient EHR. [accessed 2019 Dec 27]. Available at: https://www.academia.edu/979095/Evaluation_of_LOINC_as_a_reference_terminology_for_clinical_document_types_A_case_report_of_an_outpatient_EHR.
17. Armitage P, Berry G, Matthews JN. Statistical methods in medical research. John Wiley & Sons; 2008.
18. Hartigan JA, Wong MA. Algorithm AS 136: a K-means clustering algorithm. J R Stat Soc Ser C Appl Stat 1979;28:100-8.
19. Genolini C, Alacoque X, Sentenac M, Arnaud C. kml and kml3d: R packages to cluster longitudinal data. J Stat Softw 2015;65:1-34.
20. Guerra L, Robles V, Bielza C, Larrañaga P. A comparison of clustering quality indices using outliers and noise. Intell Data Anal 2012;16:703-15.
21. Caliński T, Harabasz J. A dendrite method for cluster analysis. Commun Stat-Theory Methods 1974;3:1-27.
22. Ray S, Turi RH. Determination of number of clusters in K-means clustering and application in colour image segmentation. 4th International Conference on Advances in Pattern Recognition and Digital Techniques (ICAPRDT'99); 1999 Dec 27; Calcutta, India. Narosa Publishing House; p137-43.
23. Davies DL, Bouldin DW. A cluster separation measure. IEEE Trans Pattern Anal Mach Intell 1979;1:224-7.
24. Nelson W, Tong YL, Lee JK, Halberg F. Methods for cosinor-rhythmometry. Chronobiologia 1979;6:305-23.
25. Massin MM, Maeyns K, Withofs N, Ravet F, Gérard P. Circadian rhythm of heart rate and heart rate variability. Arch Dis Child 2000; 83:179-82.
26. Cornelissen G. Cosinor-based rhythmometry. Theor Biol Med Model 2014;11:16.
27. Tong YL. Parameter estimation in studying circadian rhythms. Biometrics 1976;32:85-94.
28. Yanai M, Satomura A, Uehara Y, Murakawa M, Takeuchi M, Kumasaka K. Circannual rhythm of laboratory test parameters among chronic haemodialysis patients. Blood Purif 2008;26:196-203.
29. Cheung AK, Yan G, Greene T, Daugirdas JT, Dwyer JT, Levin NW, et al. Seasonal variations in clinical and laboratory variables among chronic hemodialysis patients. J Am Soc Nephrol 2002;13:2345-52.
30. Usvyat LA, Carter M, Thijssen S, Kooman JP, van der Sande FM, Zabetakis P, et al. Seasonal variations in mortality, clinical, and laboratory parameters in hemodialysis patients: a 5-year cohort study. Clin J Am Soc Nephrol 2012;7:108-15.

31. Shephard RJ, Aoyagi Y. Seasonal variations in physical activity and implications for human health. Eur J Appl Physiol 2009;107:251-71.
32. Yosipovitch G, Reis J, Tur E, Blau H, Harell D, Morduchowicz G, et al. Sweat electrolytes in patients with advanced renal failure. J Lab Clin Med 1994;124:808-12.
33. Cai H, Shu XO, Hebert JR, Jin F, Yang G, Liu DK, et al. Variation in nutrient intakes among women in Shanghai, China. Eur J Clin Nutr 2004;58:1604-11.
34. Smolková B, Dusinská M, Raslová K, McNeill G, Spustová V, Blazícek P, et al. Seasonal changes in markers of oxidative damage to lipids and DNA; correlations with seasonal variation in diet. Mutat Res 2004;551:135-44.
35. Te Dorsthorst RPM, Hendrikse J, Vervoorn MT, van Weperen VYH, van der Heyden MAG. Review of case reports on hyperkalemia induced by dietary intake: not restricted to chronic kidney disease patients. Eur J Clin Nutr 2019;73:38-45.
36. Leggat JE Jr, Orzol SM, Hulbert-Shearon TE, Golper TA, Jones CA, Held PJ, et al. Noncompliance in hemodialysis: predictors and survival analysis. Am J Kidney Dis 1998;32:139-45.
37. Kugler C, Vlaminck H, Haverich A, Maes B. Nonadherence with diet and fluid restrictions among adults having hemodialysis. J Nurs Scholarsh 2005;37:25-9.
38. Shemin D, Bostom AG, Laliberty P, Dworkin LD. Residual renal function and mortality risk in hemodialysis patients. Am J Kidney Dis 2001;38:85-90.
39. Lee JE, Kim HJ, Lee MJ, Kwon YE, Kyung MS, Park JT, et al. Comparison of dietary intake patterns in hemodialysis patients by nutritional status: a cross-sectional analysis. Kidney Res Clin Pract 2020;39:202-12.
40. Ong SW, Jassal SV, Miller JA, Porter EC, Cafazzo JA, Seto E, et al. Integrating a smartphone-based self-management system into usual care of advanced CKD. Clin J Am Soc Nephrol 2016;11:1054-62.

https://doi.org/10.3349/ymj.2021.62.4.315