

ORIGINAL ARTICLE

Nutrition

The prevalence of predialysis hyperkalemia and associated characteristics among hemodialysis patients: The RE-UTILIZE study

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Abstract

Introduction: Hyperkalemia (HK), defined as serum potassium (K^+) >5.0 mEq/L, is an independent predictor of mortality in patients on maintenance hemodialysis (HD). This study investigated the annual prevalence of HK and examined patient characteristics potentially associated with a higher annual HK prevalence.

Methods: This retrospective observational cohort study used Dialysis Outcomes and Practice Patterns Study (DOPPS) survey data from US patients undergoing in-center HD thrice weekly from 2018 to 2019. The primary endpoint was the proportion of patients with any predialysis HK ($K^+ >5.0$ mEq/L) within 1 year from the index date (date of DOPPS enrollment), using the first hyperkalemic K^+ value. Secondary endpoints were the proportion of patients with moderate-to-severe ($K^+ >5.5$ mEq/L) or severe ($K^+ >6.0$ mEq/L) HK.

Findings: Overall, 9347 patients on HD were included in this analysis (58% male and 49% aged >66 years). Any predialysis HK ($K^+ >5.0$ mEq/L) occurred in 74% of patients within 1 year of the index date, 52% within 3 months, and 38% within 1 month. The annual prevalence of moderate-to-severe and severe HK was 43% and 17%, respectively. Recurrent HK (at least two $K^+ >5.0$ mEq/L within 1 year) occurred in 60% of patients, and 2.8% of patients were prescribed an oral K^+ binder. Multivariable logistic regression analysis showed younger age, female sex, Hispanic ethnicity, and renin-angiotensin-aldosterone system inhibitor use were significantly associated with a higher annual prevalence of any predialysis HK, while Black race, obesity, recent initiation of HD, and dialysate K^+ bath concentration ≥ 3 mEq/L were associated with a lower prevalence of HK.

Data from this study were previously presented at the National Kidney Foundation: Spring Clinical Meetings (Virtual Meeting, April 6–10, 2021) as a poster presentation.

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Discussion: The annual prevalence of predialysis HK and recurrence were high among US patients on HD, whereas oral K⁺ binder use was low. Further studies are needed to understand the impact of dialysate K⁺ bath concentrations on predialysis HK among patients on HD.

KEYWORDS

Dialysis Outcomes and Practice Patterns Study, hemodialysis, hyperkalemia, prevalence

INTRODUCTION

Hyperkalemia (HK), generally defined as serum potassium (K⁺) concentrations of >5.0 mEq/L, is a common complication of chronic kidney disease (CKD), particularly in patients with end-stage renal disease (ESRD) receiving maintenance hemodialysis (HD).¹ In patients with CKD, HK is primarily caused by a decline in glomerular filtration rate and therefore reduced excretion of excess K⁺.² In patients on HD, the current management of HK includes reduction of dialysate K⁺ concentrations, increased frequency of dialysis sessions, restriction of dietary K⁺, and avoidance of medications that increase serum K⁺ levels.³

Hyperkalemia is potentially life-threatening as it may cause ventricular arrhythmias and cardiac arrest.¹ In patients on HD, HK is an independent predictor of mortality.^{4–6} Predialysis serum K⁺ concentrations of ≥5.5,⁴ ≥5.6,⁵ and ≥5.7 mEq/L¹ have been associated with an increased risk of all-cause mortality. In addition, higher predialysis K⁺ concentrations are associated with greater acute reductions in serum K⁺ during and immediately after HD,⁷ which may increase the risk of cardiac arrhythmia.⁸

The reported prevalence of HK in patients on HD has varied between epidemiologic studies from different regions, including the United States (US) and Europe.^{2,9–11} Some of the variations may be due to differences in measured durations (e.g., monthly vs. annual prevalence), threshold laboratory K⁺ values (e.g., >5.0 vs. >5.5 vs. >6.0 mEq/L), or number of laboratory K⁺ values used to define HK (e.g., one vs. two). The Dialysis Outcomes and Practice Patterns Study (DOPPS) is a prospective cohort study investigating practice-related outcomes for patients on HD in >20 countries. Regularly updated, publicly available information on the monthly prevalence of HK is available from the DOPPS Practice Monitor, based on data from approximately 11,000 HD patients in >200 facilities.¹² More detailed information beyond the recent analyses is needed to estimate the annual prevalence of predialysis HK and to identify differences in HK prevalence between subgroups of patients on HD. It is unclear if the estimated prevalence of predialysis HK is impacted by the use of any one laboratory K⁺ value to define HK (e.g., K⁺ >5.0 mEq/L) any time over a 1-year follow-up

period, and whether the estimated prevalence of HK differs depending on the day of the blood sampling, such as before the first (Monday/Tuesday), second (Wednesday/Thursday), or third (Friday/Saturday) HD session.

Patient characteristics associated with increased prevalence of HK among patients with nondialysis-dependent CKD include advanced CKD stage, estimated glomerular filtration rate < 15 mL/min/1.73 m², elevated serum creatinine, proteinuria, treatment with renin-angiotensin-aldosterone system inhibitors (RAASis), diabetes, cancer, and age.^{13–16} However, there are limited data on predictive characteristics for predialysis HK in ESRD patients on HD.

The aim of this study was to provide an expanded analysis of publicly available information to increase our understanding of the annual prevalence of HK over time and in various patient subgroups. This study also examined patient characteristics associated with higher annual prevalence of predialysis HK in HD patients.

METHODS

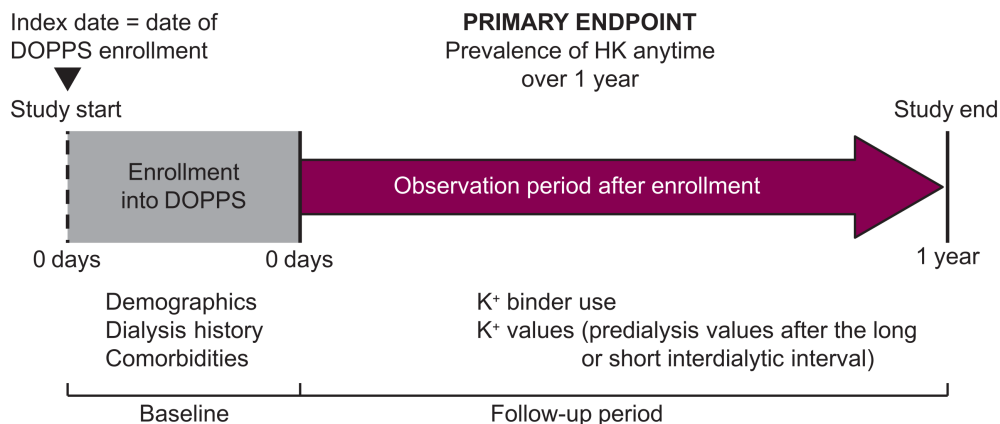
Study design and objectives

RE-UTILIZE was a retrospective observational cohort study that used DOPPS survey data from US patients who initiated in-center thrice-weekly HD from 2018 to 2019 (Figure 1).

DOPPS is an international prospective study of adult patients (aged ≥18 years) treated with in-center HD. In each country, a sample of maintenance HD patients was randomly selected from a nationally representative sample of dialysis facilities. Anonymized data on demographics, laboratory values, dialysis history, K⁺ binder use, and comorbidities were collected by a facility coordinator at each dialysis center using a standardized chart abstraction procedure. This study utilized a de-identified limited DOPPS data set for the US, pursuant to a data use and licensing agreement between AstraZeneca and Arbor Research Collaborative for Health.

The objectives of the study were to: (1) describe the prevalence of HK (defined using the first predialysis

FIGURE 1 Study design and timeline. DOPPS, Dialysis Outcomes and Practice Patterns Study; HK, hyperkalemia; K⁺, potassium [Color figure can be viewed at wileyonlinelibrary.com]



K⁺ >5.0 mEq/L any time over 1 year) in all patients on HD (primary); (2) identify patient characteristics associated with higher annual prevalence of HK (secondary); and (3) describe the prevalence of HK using the first predialysis K⁺ value at the first, second, or third dialysis session; the prevalence of predialysis HK over a 1- or 3-month period; and the recurrence of predialysis HK over a 1-year period (exploratory).

The study was considered exempt from Institutional Review Board approval as dictated by Title 45 Code of Federal Regulations, part 46 of the US, specifically 45 CFR 46.101(b) (4). In accordance with the Health Insurance Portability and Accountability Act Privacy Rule, disclosed DOPPS data were considered anonymized per 45 CFR 164.506(d) (2)(ii)(B) through the “Expert Determination” method; no individual patient information was reported.

Study population

Not all patients enrolled in DOPPS were included in the RE-UTILIZE study. To be included in the study, US-based patients undergoing in-center HD during 2018 through 2019 were required to have: (1) ≥1 year of enrollment in DOPPS; and (2) ≥1 nonmissing monthly laboratory K⁺ value within 1 year of the index date. Therefore, all eligible patients were initially enrolled in DOPPS in 2018 or 2019; data from 2020 represented a partial year, and no patients enrolled in DOPPS in 2020 were included as full-year 2020 data were not available at the time of data analysis. Patients without laboratory K⁺ values or who had been enrolled in DOPPS for <1 year were excluded (Figure 2).

Study outcomes

The primary endpoint was the proportion of patients who experienced any predialysis HK (K⁺ >5.0 mEq/L)

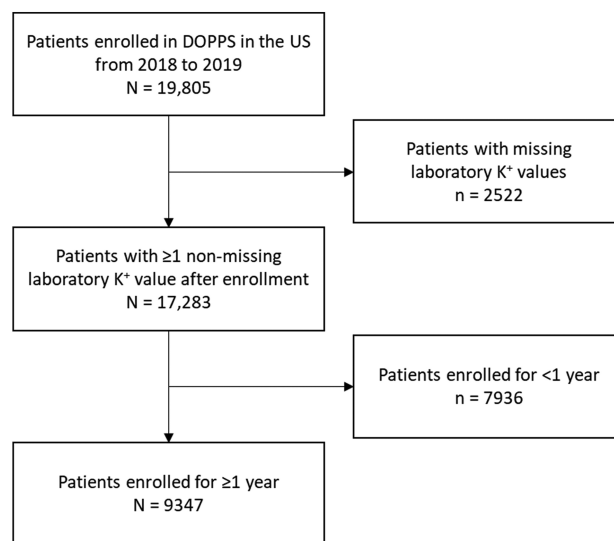


FIGURE 2 Diagram of patient flow in the study. DOPPS, Dialysis Outcomes and Practice Patterns Study; K⁺, potassium; US, United States

any time over a 1-year period from the index date, using the first monthly laboratory K⁺ value that met the definition of HK. The predialysis K⁺ values were obtained after the long or short interdialytic interval.

The secondary endpoints were the proportion of patients experiencing moderate-to-severe HK (K⁺ >5.5 mEq/L) or severe HK (K⁺ >6.0 mEq/L) any time over a 1-year period from the index date, using the first laboratory K⁺ value that met the respective definitions of moderate-to-severe or severe HK. The association between patient characteristics (i.e., age category, sex, race, ethnicity, diabetic ESRD as primary cause of dialysis, year of first dialysis at the DOPPS facility, and comorbidities) and the prevalence of HK was also examined.

Exploratory endpoints were the recurrence of predialysis HK over 1 year, where recurrence was defined as at least two laboratory K⁺ values meeting the HK

definition after the first K^+ value met the HK definition, and the proportion of patients experiencing HK, moderate-to-severe HK, or severe HK any time within 1 and 3 months of the index date, and any time over a 1-year period using the first monthly K^+ value that met the definition of HK from the first (Monday/Tuesday), second (Wednesday/Thursday), and third (Friday/Saturday) HD session. Although rare, some patients had blood sampling on Sundays.

Statistical analysis

Descriptive statistics (i.e., counts and percentages) were used to analyze the primary, secondary, and exploratory endpoints; no formal statistical hypotheses were tested for the primary and exploratory endpoints. In these analyses, median (interquartile range [IQR]) and mean \pm standard deviation (SD) were used to express the time in days from index date to the date of the primary or secondary endpoint, and mean \pm SD was used to describe K^+ values used to define HK.

To minimize bias, the analysis was limited to patients with ≥ 1 non-missing monthly laboratory K^+ value so that the estimate of HK prevalence did not include patients without K^+ values.

A sample size of 9347 patients was considered adequate to meet the study needs. As the primary endpoint measure was a proportion, the worst case scenario for precision would occur when the proportion was 50%. For an evaluable sample size of 9347 patients, the margin of error was 1.0%; no formal power considerations were needed.

For the secondary endpoints, hypothesis testing was conducted using logistic regression models to analyze patient characteristics associated with the annual prevalence of HK. Adjusted odds ratios (ORs) with 95% confidence intervals (CIs) and P-values were reported for selected patient characteristics, including age category, sex, race, ethnicity, and diabetes as primary cause of ESRD, body mass index (BMI), RAASi prescription, year of first dialysis at the DOPPS facility, dialysis session length, dialysate K^+ bath concentration, albumin level, and comorbidities. For multivariable regression analysis, the first K^+ value that met the definition of HK was included in the analysis as the outcome of interest, and the reference level was the first K^+ value that did not meet the definition of HK over 1 year among patients who never met the definition of HK. The unit of analysis was the distinct combination of patient and facility. The regression models took into account facility clustering. All statistical analyses were carried out using SAS

version 9.4. A *p* value of 0.05 was considered to indicate statistical significance.

RESULTS

Patients

Between 2018 and 2019, 19,805 patients in the US undergoing in-center thrice-weekly HD were initially enrolled in DOPPS and 9347 patients were included in this analysis (Figure 2). Of these patients, 58% were male, 49% were aged >66 years, and 56% first underwent HD at the DOPPS facility before 2018 (Table 1). The most common comorbidities were hypertension (80%), diabetes (64%), and hyperlipidemia (62%); diabetes was the primary cause of ESRD in 41% of patients. A low proportion of patients (2.8%) were prescribed an oral K^+ binder therapy.

Prevalence and recurrence of predialysis HK

The prevalence of any predialysis HK within 1 year of DOPPS enrollment was 74%, when HK was defined as the first monthly $K^+ >5.0$ mEq/L value on any day (Figure 3). Any predialysis HK occurred in 38% of patients within 1 month and 52% within 3 months of the index date (Figure 3). The median (IQR) time from index date to the first $K^+ >5.0$ mEq/L value was 60 (24–144) days (Table 2). Of the laboratory values used to define any HK ($K^+ >5.0$ mEq/L), the mean \pm SD K^+ concentration was 5.4 ± 0.36 mEq/L.

Moderate-to-severe predialysis HK occurred in 15% of patients within 1 month, 24% within 3 months, and 43% within 1 year of the index date and severe HK in 4%, 8%, and 17% of patients, respectively (Figure 3). The median (IQR) time from index date to first laboratory K^+ value >5.5 mEq/L was 109 (44–205) days and to first laboratory K^+ value >6.0 mEq/L was 142 (61–241) days (Table 2). The mean K^+ concentration was 5.9 ± 0.33 mEq/L for moderate-to-severe HK and 6.4 ± 0.34 mEq/L for severe HK.

Among patients with any predialysis HK ($K^+ >5.0$ mEq/L), the proportion of patients with moderate ($K^+ >5.5$ to ≤ 6.0 mEq/L) or severe ($K^+ >6.0$ mEq/L) predialysis HK increased over time (Figure S1). Among those with any predialysis HK within 1 month ($n = 3531$), 27% had moderate HK and 11% had severe HK. Of the patients who had predialysis HK within 3 months ($n = 4861$), 31% had moderate HK and 15% had severe HK, and of those who

TABLE 1 Patient demographics and clinical characteristics

Characteristics, <i>n</i> (%)	<i>N</i> = 9347
Year of first DOPPS enrollment	
2018	8133 (87.0)
2019	1214 (13.0)
Age category, years	
≤50	1577 (16.9)
51–65	3159 (33.8)
66–80	3414 (36.5)
≥81	1197 (12.8)
Sex	
Male	5425 (58.0)
Female	3914 (41.9)
Unknown/missing	8 (0.1)
Race	
Black	3253 (34.8)
Non-Black	4458 (47.7)
Unknown/missing	1636 (17.5)
Ethnicity	
Hispanic	388 (4.2)
Non-Hispanic	2587 (27.7)
Unknown/missing	6372 (68.2)
BMI	
<30 kg/m ²	6588 (70.5)
≥30 kg/m ²	2759 (29.5)
Serum albumin	
<3.4 g/dL	2866 (30.7)
≥3.4 g/dL	6481 (69.3)
Primary cause of ESRD	
Diabetes	3791 (40.6)
All other causes	4471 (47.8)
Unknown/missing	1085 (11.6)
Year of first dialysis at DOPPS facility	
Prior to 2018	5239 (56.1)
2018	3732 (39.9)
2019	376 (4.0)
Dialysate K ⁺ bath concentration	
<3 mEq/L	8416 (90.0)
≥3 mEq/L	931 (10.0)
Dialysis session duration	
<180 min	3865 (41.4)
≤180 min	5482 (58.6)
At least one prescription for oral K ⁺ binder	263 (2.8)
Concomitant RAASi medication	
Yes	688 (7.4)
No	8659 (92.6)

(Continues)

TABLE 1 (Continued)

Characteristics, <i>n</i> (%)	<i>N</i> = 9347
Comorbidities	
Hypertension	7507 (80.3)
Diabetes	5947 (63.6)
Hyperlipidemia	5803 (62.1)
Cardiovascular disease	3915 (41.9)
Mental health disorder	2216 (23.7)
Arrhythmia	801 (8.6)
Cerebrovascular disease	703 (7.5)
Cancer	501 (5.4)
Smoker	380 (4.1)
Substance use disorder	105 (1.1)

Abbreviations: BMI, body mass index; DOPPS, Dialysis Outcomes and Practice Patterns Study; ESRD, end-stage renal disease; K⁺, potassium; RAASi, renin-angiotensin-aldosterone system inhibitor.

experienced any predialysis HK within 1 year (*n* = 6910), 35% had moderate HK and 23% had severe HK.

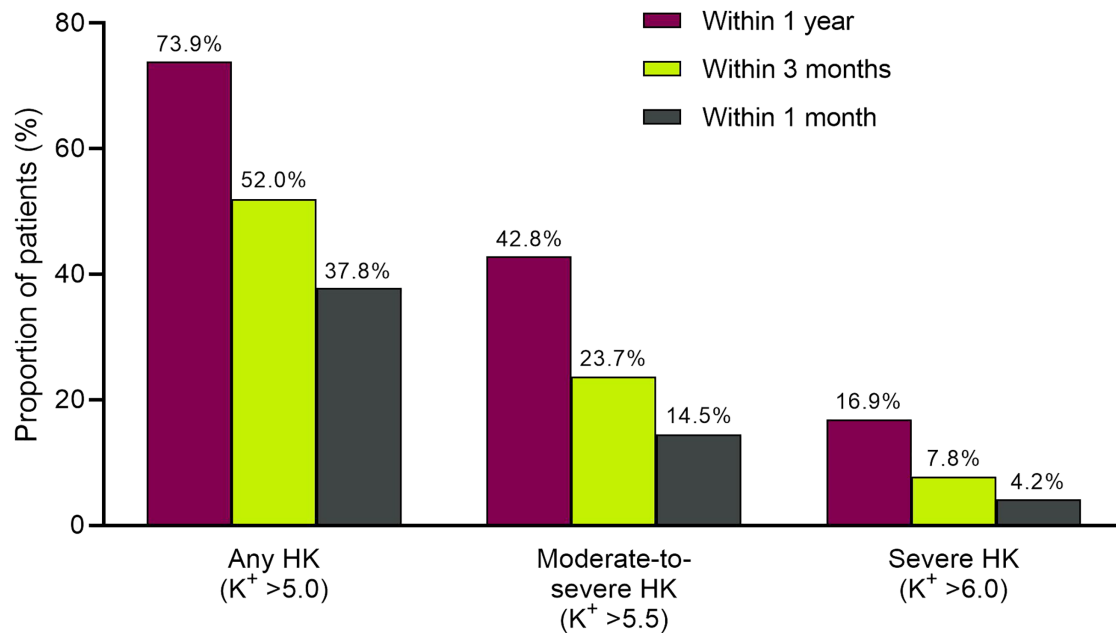
In the exploratory analysis, recurrent predialysis HK with a second laboratory K⁺ value >5.0 mEq/L occurred in 60% of patients; 48% and 39% of patients had a third and fourth laboratory K⁺ value >5.0 mEq/L (Figure 4). A second laboratory K⁺ value meeting the definition of moderate-to-severe (K⁺ >5.5 mEq/L) and severe (K⁺ >6.0 mEq/L) HK was observed in 25% and 7% of patients, respectively. The annual prevalence of any predialysis HK, moderate-to-severe HK, and severe HK showed limited variation when using the first K⁺ laboratory values from the first, second, or third dialysis session of the week (Figure 5). Since blood sampling on Sundays was less common, predialysis prevalence of HK on Sundays is not shown.

The prevalence of any predialysis HK was high in patients with or without RAASi therapy (77.8% vs. 72.5%). Of those patients who were receiving a RAASi (*n* = 688), 502 patients (73.0%) initiated RAASi therapy after developing HK.

Patients receiving an oral K⁺ binder had a higher prevalence of predialysis HK compared with those not receiving a K⁺ binder (92.8% vs. 73.4%). Of those receiving a K⁺ binder (*n* = 263), the majority (*n* = 223; 84.8%) initiated K⁺ binder therapy after developing HK.

Factors associated with annual predialysis HK prevalence

In the multivariable logistic regression analysis of predialysis HK, younger age categories (i.e., ≤50, 51–65, and 66–80 years) were significantly associated with



n	Any HK (K ⁺ >5.0)			Moderate-to-severe HK (K ⁺ >5.5)			Severe HK (K ⁺ >6.0)		
	1 year	3 months	1 month	1 year	3 months	1 month	1 year	3 months	1 month
	6910	4861	3531	4000	2213	1351	1575	730	393

FIGURE 3 Prevalence of predialysis HK based on the first monthly K⁺ value >5.0, >5.5, and >6.0 mEq/L within 1 year, 3 months, and 1 month of initial DOPPS enrollment. DOPPS, Dialysis Outcomes and Practice Patterns study; HK, hyperkalemia; K⁺, potassium [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 2 Time from index date to incidence of predialysis hyperkalemia (first K⁺ value >5.0, >5.5, or >6.0 mEq/L)

Time from index date to first K ⁺ value used to define HK, days	>5.0 mEq/L	>5.5 mEq/L	>6.0 mEq/L
Mean ± SD	95.4 ± 91.4	131.5 ± 101.9	155.8 ± 105.7
Median (IQR)	60 (24–144)	109 (44–205)	142 (61–241)
Range	0–365	0–365	0–365

Abbreviations: HK, hyperkalemia; IQR, interquartile range; K⁺, potassium; SD, standard deviation.

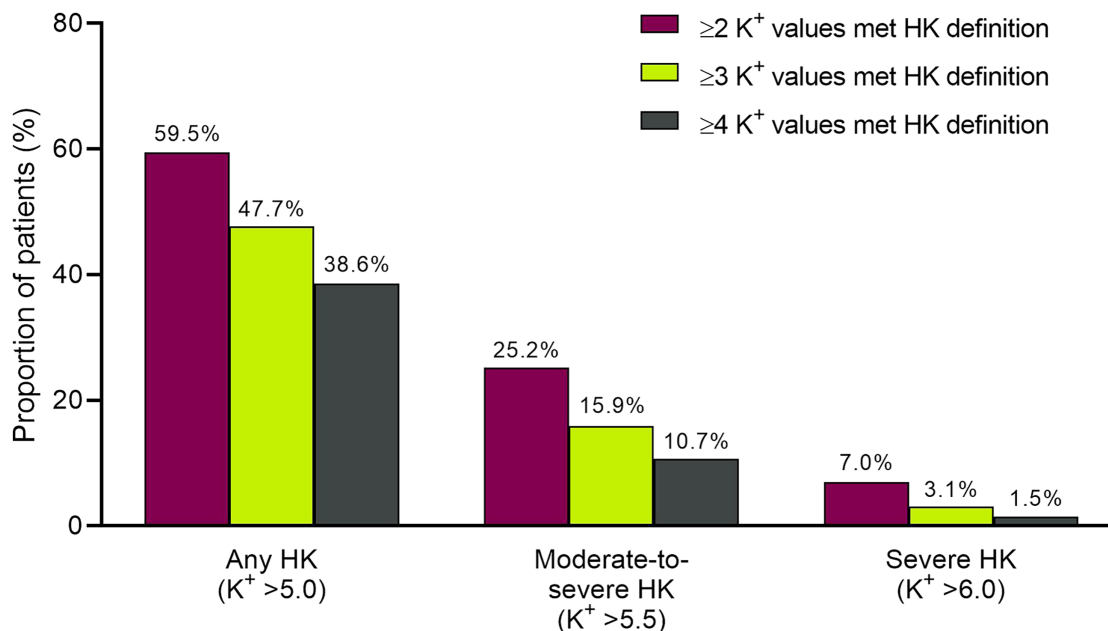
higher odds of any predialysis HK versus age ≥81 years ($p < 0.0001$ for all comparisons; Figure 6). Female sex (vs. male; $p = 0.04$), Hispanic ethnicity (vs. non-Hispanic; $p = 0.037$), and concomitant RAASi medication ($p = 0.001$) were also significantly associated with higher odds of any predialysis HK. Factors showing significant association with a lower odds of any predialysis HK were Black race (vs. non-Black; $p = 0.0004$), recent initiation of dialysis at DOPPS facility (2018–2019 vs. pre-2018; $p = 0.0002$), obesity (BMI ≥30 kg/m²; $p = 0.009$), and dialysate K⁺ bath concentration ≥3 mEq/L ($p < 0.0001$).

DISCUSSION

In this study of patients on in-center HD in the US, the prevalence of predialysis HK was high, with serum K⁺

concentrations of >5.0, >5.5, and >6.0 mEq/L reported in 74%, 43%, and 17% of patients, respectively, within 1 year, 52%, 24%, and 8% of patients, respectively, within 3 months, and 38%, 15%, and 4% of patients, respectively, within 1 month. The recurrence of predialysis HK was also high; 60% of patients had a second laboratory K⁺ value of >5.0 mEq/L. In contrast with the high prevalence and recurrence of predialysis HK, a low proportion of patients (<3%) were prescribed oral K⁺ binder therapy. Moreover, among patients with any predialysis HK (K⁺ >5.0 mEq/L), the proportion of patients with moderate (K⁺ >5.5 to ≤6.0 mEq/L) or severe (K⁺ >6.0 mEq/L) predialysis HK increased over time, occurring in a total of 38% of patients within 1 month, 46% within 3 months, and 58% within 1 year.

The data illustrated in Figures 3–5 show that the prevalence of predialysis HK increased over time



n	Any HK (K ⁺ >5.0)			Moderate-to-severe HK (K ⁺ >5.5)			Severe HK (K ⁺ >6.0)		
	≥2 K ⁺	≥3 K ⁺	≥4 K ⁺	≥2 K ⁺	≥3 K ⁺	≥4 K ⁺	≥2 K ⁺	≥3 K ⁺	≥4 K ⁺
	5558	4461	3605	2353	1482	1002	655	288	141

FIGURE 4 Recurrence of predialysis HK based on second, third, and fourth monthly K⁺ value >5.0, >5.5, and >6.0 mEq/L within 1 year of initial DOPPS enrollment. DOPPS, Dialysis Outcomes and Practice Patterns Study; HK, hyperkalemia; K⁺, potassium [Color figure can be viewed at wileyonlinelibrary.com]

(i.e., over 1 month, 3 months, and 1 year), and that a significant proportion of HD patients experience recurrent predialysis HK, despite long-term dialysis therapy. This suggests that many patients on HD may not be receiving optimal therapy for hyperkalemia, and that long-term oral K⁺ binder treatment may improve K⁺ homeostasis in this patient population. Although the degree of HK severity is associated with increased mortality risk,¹ further studies are needed to determine if recurrent predialysis HK also increases the risk of mortality in HD patients. Our results also show that the prevalence of predialysis HK remained high irrespective of whether the first K⁺ laboratory values used to determine HK were collected before the first, second, or third dialysis session of the week.

The high prevalence of predialysis HK in this study is higher than that reported on the publicly available DOPPS Practice Monitor website, where the weighted prevalence of serum K⁺ ≥5.0 mEq/L in August 2020, based on the most recent single monthly predialysis serum K⁺ value, was 38.8%.¹² Previous retrospective database studies of US patients on dialysis have also reported a lower prevalence of HK than our study with an HK prevalence of 33% (when defined as K⁺ ≥5.0 mEq/L) among HD patients,¹¹ an annual prevalence among dialysis patients of 43.5% in 2014 (K⁺ >5.0 mEq/L),² and

ranging from 50.2 to 52.8% between 2010 and 2014 (K⁺ ≥5.0 mEq/L).⁹ Some studies that used higher K⁺ concentration thresholds reported a much lower prevalence of HK, including a previous international DOPPS analysis in which the prevalence of HK (defined as K⁺ >6.0 mEq/L) was 6.3% in the US and 20.0% in Europe.¹⁰

In addition to the varying K⁺ concentration thresholds used to define HK, differences in observed HK prevalence between studies may be due to differences in methods used to determine HK. For example, using one laboratory K⁺ value (as in this study) may increase the annual prevalence estimate compared with using two laboratory values.² Our DOPPS study, consistent with this theory, reported higher annual prevalence of K⁺ >5.0 mEq/L when using one laboratory K⁺ value (73.9%) than a previous US retrospective study that used at least two laboratory values (43.5%), although the latter estimate also included patients on peritoneal dialysis.²

The prevalence of predialysis HK in our study was >70% regardless of RAASi use, but the odds of any predialysis HK were significantly higher in patients with concomitant RAASi use than in those not on RAASi therapy, and appeared to be higher among patients on an oral K⁺ binder therapy than in those not on K⁺ binder therapy. However, these results should be interpreted with

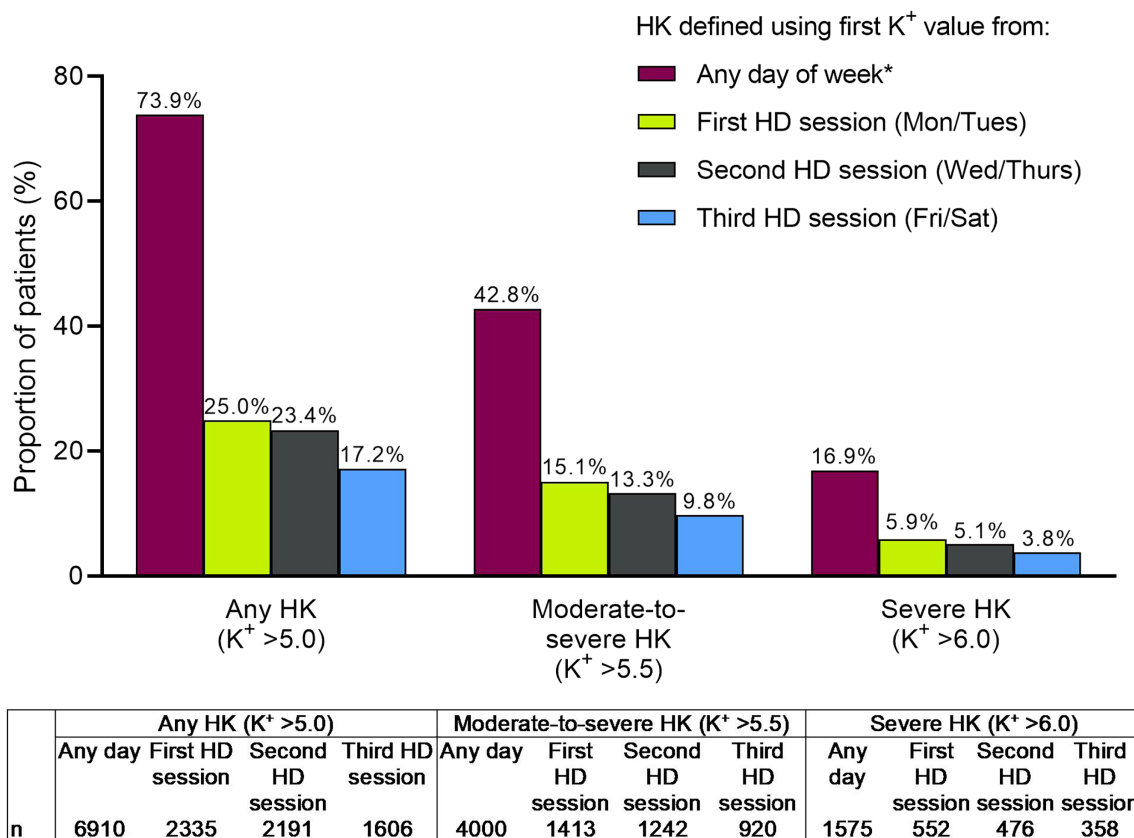


FIGURE 5 Annual prevalence of predialysis HK based on first monthly K⁺ value >5.0, >5.5, and >6.0 mEq/L from any day of the week and on the first, second, and third HD session. *Includes patients with Sunday blood sampling. HD, hemodialysis; HK, hyperkalemia; K⁺, potassium [Color figure can be viewed at wileyonlinelibrary.com]

caution as the higher HK prevalence in patients on K⁺ binder therapy may simply indicate that the medication is often initiated after HK develops, rather than meaning that K⁺ binder therapy did not work or led to an increased prevalence of HK.

In contrast to the low rate of oral K⁺ binder use observed in our study, a recent French registry study reported a prescribing rate for K⁺ binders of 37% among patients who initiated dialysis between 2010 and 2013.¹⁷ However, a previous DOPPS study showed that use of K⁺ binders varies widely between different countries, with prescription rates of 42% in France, 25% in Sweden, 14% in Belgium, 13% in Italy, and 5% in Canada.¹⁸ The low K⁺ binder prescription rate in Canada is consistent with that observed in our study.

In our study population, age ≤80 years, female sex, Hispanic ethnicity, and concomitant RAASi medication were associated with higher odds of predialysis HK, whereas Black race, recent dialysis initiation, obesity, and dialysate K⁺ bath concentrations ≥3 mEq/L were associated with lower odds of predialysis HK. Multiple factors contribute to determining serum K⁺ in patients on HD, including dietary K⁺ intake, certain medications (e.g., RAASi, nonsteroidal anti-inflammatory drugs, K⁺-

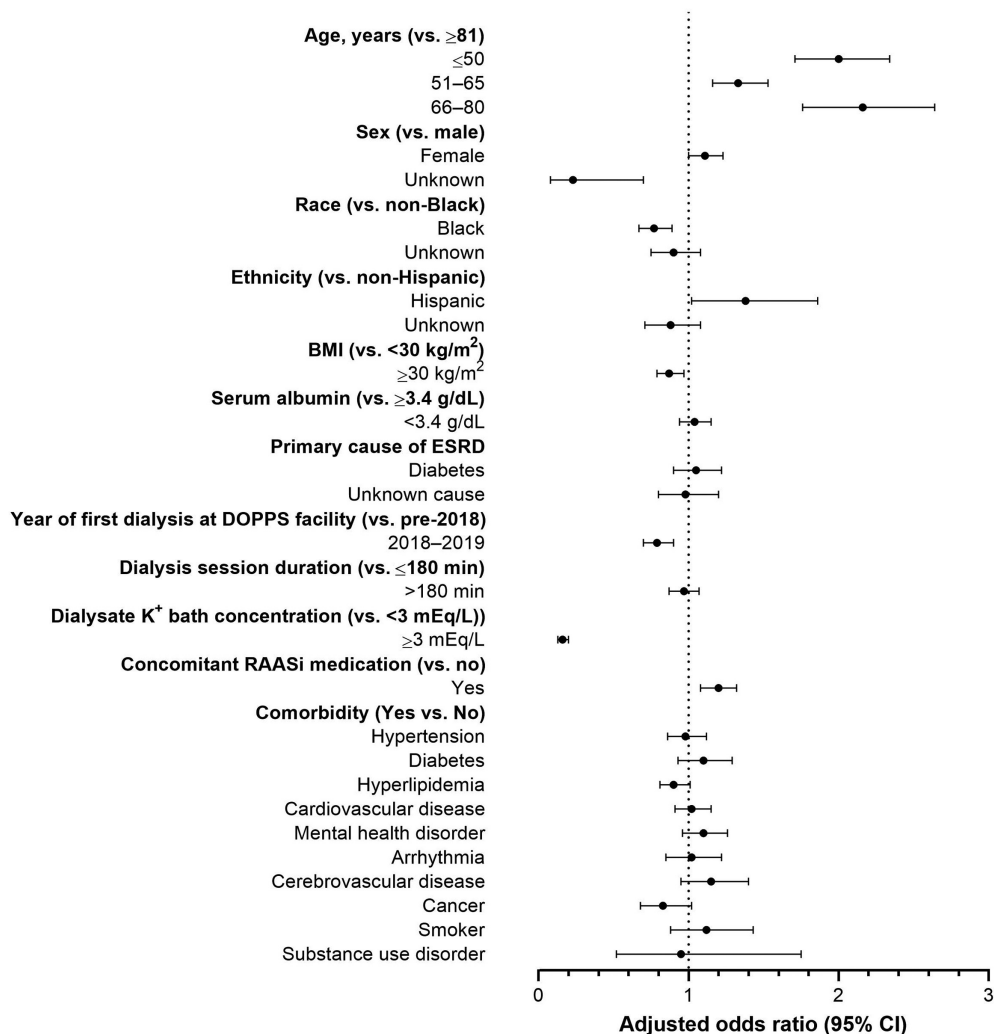
sparing diuretics, and digoxin), dialysate K⁺ bath concentrations, dialysis session length, and the effectiveness of K⁺ removal.³

One potential explanation for the lower odds of predialysis HK in patients with newly initiated dialysis may be the presence of residual kidney function, which declines over time in patients on maintenance HD.¹⁹ Other possible explanations include stringent dietary K⁺ and/or protein restriction as well as decreased prevalence of RAASi prescriptions and increased diuretic prescribing (leading to kaliuresis) in patients with stage 5 CKD.²⁰

Our study also showed that obesity was associated with lower odds of predialysis HK. This finding is consistent with a previous registry study of patients with CKD, which found that low BMI (<18.5 kg/m²) was associated with increased odds of HK (OR, 1.60; 95% CI, 1.23–2.08) and high BMI (>30 kg/m²) with lower odds of HK (OR, 0.77; 95% CI, 0.70–0.85).²¹ One explanation of the lower risk of HK in patients with obesity may be due to the increase in hyperaldosteronism among patients with high BMI, which leads to an increase in K⁺ excretion.²²

In our study, a dialysate K⁺ bath concentration ≥ 3 mEq/L was associated with lower odds of predialysis HK. Similarly, a previous DOPPS study found that after

FIGURE 6 Forest plot of patient factors associated with annual prevalence of any predialysis HK (first laboratory K^+ >5.0 mEq/L value). BMI, body mass index; CI, confidence interval; DOPPS, Dialysis Outcomes and Practice Patterns Study; ESRD, end-stage renal disease; HK, hyperkalemia; K^+ , potassium; RAASI, renin-angiotensin-aldosterone system inhibitor



adjusting for confounding variables, there was an inverse relationship between dialysate K^+ bath concentrations and predialysis serum K^+ levels, with a change of -0.25 (95% CI, -0.26 to -0.24) mEq/L in serum K^+ per 1-mEq/L increase in dialysate K^+ bath concentration.²³ However, this effect is almost certainly confounded by indication (i.e., patients with lower predialysis serum K^+ are prescribed higher dialysate K^+ bath concentrations), as an instrumental variable analysis to account for this bias in the previous study showed a minimal effect of dialysate K^+ concentration on serum K^+ of $+0.09$ (95% CI, 0.05–0.14) mEq/L per 1-mEq/L increase in dialysate K^+ concentration.²³

Our study found that younger age was associated with increased odds of predialysis HK. This finding is consistent with a previous study of the prevalence of HK ($K^+ \geq 5.5$ mEq/L) in HD patients, which reported a higher HK prevalence in patients aged 18–44 years versus those aged ≥ 75 years (18.7 vs. 12.6 events per 100 patient-months).¹ Potential explanations for this observation include a more robust protein intake (most protein sources are also a good source of potassium) in younger

patients compared with older patients; a recent US Renal Data System (USRDS) report showed a greater proportion of younger patients had normal serum albumin levels compared with older patients.²⁴ Female sex was also associated with increased odds of predialysis HK compared with male sex; this difference has yet to be explained, other than possible variations in dietary K^+ intake.

Our study did not evaluate hyperkalemia hospitalizations; however, USRDS data showed that in patients with stage 5 CKD, the risk of hospitalization for hyperkalemia was greater in patients aged 70–84 years compared with those aged ≥ 85 years, and interestingly, in patients with stage 5 CKD, the rate of hospitalization for hyperkalemia was 5.8/1000 person-years in females versus 7.0/1000 person-years in males.²⁵ Given these differences in patient factors associated with predialysis HK, further long-term studies with larger populations are needed to confirm the risk factors for predialysis HK in patients on HD.

In a previous study of patients on HD, HK was more likely to occur the day after the long interdialytic interval

versus the day after the short interdialytic interval.¹ In the general population, HK prevalence was consistently higher among individuals aged ≥ 65 years versus < 65 years within the same comorbidity subgroup, including patients on dialysis, indicating that age is an independent risk factor for HK.² A previous US study of patients on maintenance HD showed baseline serum K^+ concentrations were significantly higher in patients with Hispanic versus non-Hispanic ethnicity, and significantly lower in Black versus non-Black patients.²⁶ Compared with White patients, the likelihood of developing HK was higher in those with Hispanic ethnicity (OR, 1.32; 95% CI, 1.25–1.39) and lower in Black patients (OR, 0.58; 95% CI, 0.55–0.62). The reasons for these ethnic/racial differences in serum K^+ concentrations and HK prevalence in HD patients are unclear, but may be related to differences in diet between groups.²⁶ In previous studies of HD patients, factors associated with lower odds of HK included plasma sodium level and diuretic use.^{27,28}

The DOPPS has advantages over other data sources; it provides a more nationally representative sample of HD patients from dialysis centers than a single large dialysis organization, and includes more detailed data than most registries and administrative databases.²⁹ However, the use of DOPPS data is associated with some limitations. Due to the retrospective, observational nature of this analysis, confounding variables are possible, and any causal associations between HK and patient factors cannot be determined. The study was limited to HD patients with available serum K^+ values in the DOPPS database, and therefore may not be generalizable to all US patients on HD or to those without available laboratory data. In addition, as laboratory values are not measured centrally, nonstandardized testing may have introduced measurement errors²⁹ and laboratory testing may be driven by the presence of HK symptoms, thereby leading to an overestimate of HK prevalence (i.e., selection bias). However, as serum K^+ measurement is a component of the routine laboratory panel, this bias is likely to be small. Lastly, our study did not evaluate the association between interdialytic interval length and predialysis HK since the dialysis schedule and interdialytic interval duration of patients was not collected within DOPPS.

CONCLUSIONS

The prevalence and recurrence of predialysis HK ($K^+ > 5.0$ mEq/L) was high among US patients on HD, whereas the proportion of patients who were prescribed a K^+ binder was low. Even if all K^+ binder prescriptions were for patients with predialysis HK, the low rate of K^+

binder prescribing suggests patients may be under-treated with oral binders during nondialysis days, although further data from outcomes studies are needed to confirm this; any such treatment pattern is likely to be episodic given the high recurrence rates. A higher annual prevalence of predialysis HK was observed in patients aged ≤ 80 years, females, patients with Hispanic ethnicity, and those on concomitant RAASi medications. Further studies are needed to understand the impact of additional factors, such as dialysate K^+ bath concentrations, on predialysis HK prevalence in HD patients.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the analysis and interpretation of the study data, contributed to the drafting of the manuscript, and provided their final approval of the version to be published. All authors are accountable for all aspects of the work.

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DISCLOSURES

All authors are shareholders and full-time employees of AstraZeneca. As such, the authors have a potential conflict of interest related to novel potassium-lowering drugs.

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SUPPORTING INFORMATION

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