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Hyperkalemia Risk with Finerenone in Diabetic Kidney Disease: A Real-World Analysis from the FINE-TURK Cohort

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Abstract

Background: Finerenone is associated with a lower, yet clinically relevant, risk of hyperkalemia compared with steroidal mineralocorticoid receptor antagonists in diabetic kidney disease (DKD) trials. However, real-world data on hyperkalemia and its associated factors are lacking. **Methodology:** FINE-TURK is a national, observational cohort of DKD patients who were initiated on finerenone. Eligible adults were included; demographic, clinical, and laboratory data were evaluated.

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The primary outcome (PO) was hyperkalemia risk signal (potassium ≥ 5.0 mEq/L), and the secondary outcome (SO) was clinically meaningful hyperkalemia (potassium ≥ 5.5 mEq/L). Multivariate logistic regression (LR) was used to define features associated with both PO and SO. LR, random forest (RF), gradient boosting, and CatBoost classifiers were used to define important features associated with the PO. **Results:** 699 patients were included. 259 (37.1%) reached the PO, and 51 (7.3%) reached the SO. Baseline potassium and estimated glomerular filtration rate (eGFR) were the most important variables associated with both outcomes and were consistently identified as the top features across all models. Thiazide use, presence of diabetic retinopathy, and diabetes duration were also associated with the PO. LR demonstrated the highest recall; random forest achieved the highest precision in performance. **Discussion:** Real-world data suggest that the risk of clinically meaningful hyperkalemia is similar to that in the clinical trials. In parallel with the safety analysis of clinical trials, baseline potassium and eGFR were consistently the most important factors associated with hyperkalemia risk.

Keywords: diabetes complications; diabetic nephropathies; hyperkalemia; machine learning; mineralocorticoid receptor antagonists

Introduction

Type 2 diabetes mellitus (T2DM) is one of the most important non-communicable diseases of the 21st century due to its high prevalence and significant disease burden [1,2]. The current global prevalence of diabetes is 564 million and is projected to grow to 600 million by 2035 [3]. T2DM-related kidney damage, namely diabetic kidney disease (DKD), affects up to one-third of the patients with T2DM, and it is the most common cause of chronic kidney disease (CKD) [4,5]. Besides, both T2DM and CKD are associated with adverse cardiovascular disease (CVD) outcomes [6,7]. The last 30 years have witnessed the development of three main medication groups to reduce the burden of DKD and related CVD outcomes. Renin-angiotensin-aldosterone system (RAAS) inhibition by angiotensin-converting enzyme (ACE) inhibitors [8] and angiotensin receptor blockers (ARB) [9], sodium-glucose cotransporter-2 (SGLT2) inhibitors [10,11], and a novel non-steroidal mineralocorticoid receptor (ns-MRA) antagonist, finerenone [12,13], has been shown to improve renal and CVD outcomes. These three medication groups are now constituting the backbone for the pharmacological treatment of diabetic kidney disease [14].

Finerenone is a third-generation MRA with high specificity, as well as more balanced kidney and heart distribution, resulting in significantly improved tolerability and efficacy compared to spironolactone and eplerenone [15]. Although spironolactone improves markers of DKD, its use is limited due to marked hyperkalemia risk and lack of hard outcome-based clinical trials [15,16]. Finerenone, on the other hand, has a markedly lower clinically meaningful hyperkalemia risk due, in part, to its shorter half-life but is still associated with hyperkalemia risk. Clinical practice translates this risk into a requirement for potassium follow-up four weeks after the initiation of finerenone [14].

The two major finerenone trials have demonstrated a 21.7% and 13.5% risk of finerenone-associated hyperkalemia (K^+ > 5.5 mmol/L) among patients with DKD [12,13]. A recent post-hoc safety analysis of the FIDELO-DKD study has evaluated the hyperkalemia risk with finerenone [17]. Although several independent risk factors that are associated with hyperkalemia were defined, there are concerns about potential discrepancies between trial-based risk and real-world risk [18,19], and real-world data-based hyperkalemia risk predictors are urgently needed. Real-world finerenone-associated hyperkalemia data, as well as factors associated with hyperkalemia, are scarce, and only one prior study has evaluated predictors of hyperkalemia [20]. This study aimed to investigate finerenone-associated hyperkalemia risk and its predictors, using real-world data and combining conventional statistical methods with machine learning approaches.

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Methodology

Study Design and Population

The FINE-TURK cohort is a national observational cohort that evaluated the efficacy and safety of finerenone in patients with diabetic kidney disease who receive contemporary cardio-renal-metabolic (CRM) treatments. Cohort characteristics were reported in the main study in detail [21]. Adults over the age of 18 with established T2DM and CKD who were initiated on finerenone for DKD were evaluated for eligibility. Patients were included if baseline potassium and baseline estimated glomerular filtration rate (eGFR, calculated using the CKD-EPI equation) prior to finerenone initiation, as well as follow-up potassium measurement data, were all present. Exclusion criteria included baseline potassium over 4.8 mEq/L, RAAS inhibitor duration less than four months, and SGLT2 inhibitor exposure less than four months prior to finerenone initiation. These thresholds were selected based on the FIGARO-DKD and the FIDELIO-DKD studies, which used the same criteria [12,13].

Variables of Interest

- Demographics and lifestyle: Age, sex, alcohol use, smoking, and physical activity
- Physical examination: Systolic blood pressure (SBP), body mass index (BMI)
- Comorbidities (either clinician diagnosed or patient reported): Hypertension, coronary artery disease (CAD, prior myocardial infarction or revascularization), stroke, diabetic retinopathy (DRP), diabetic peripheral sensory neuropathy, heart failure (HF), ejection fraction (EF) of patients with HF, and durations of hypertension and T2DM diagnosis.
- Contemporary CRM medications: Finerenone dose initiated (20 mg or 10 mg), current use of any SGLT2 inhibitor, duration of SGLT2 inhibitor use, use of any ACE inhibitor or ARB, presence of maximal RAAS inhibition (according to manufacturers' labels), RAAS inhibition duration, use of any glucagon-like peptide-1 (GLP-1) receptor agonist, and dipeptidyl peptidase-4 (DPP-4) inhibitor.
- Traditional CRM medications: Current use of any insulin, metformin, sulfonylurea, calcium channel blocker, beta blocker, alpha blocker, thiazide (or thiazide-like) diuretic, loop diuretic, any antihypertensive, and statin.
- Laboratory: Baseline eGFR, potassium, urinary albumin, serum sodium, albumin, uric acid, hemoglobin, and hemoglobin A1c (HbA1c) values.

Outcome Definition

The primary outcome (PO) was the hyperkalemia risk signal, which was defined as serum potassium ≥ 5.0 mEq/L at the first follow-up (month 1), or, if the first follow-up measurement was below the threshold or missing, serum potassium ≥ 5.0 mEq/L at the second follow-up (month 3). The secondary outcome (SO) was the clinically meaningful hyperkalemia, which was defined analogously using a threshold of 5.5 mEq/L. Hyperkalemia thresholds were chosen as ≥ 5.0 mEq/L and ≥ 5.5 mEq/L per latest reviews and guidelines [22,23].

Descriptive Statistics and Missing Data

Continuous variables were assessed for normality using the Shapiro–Wilk test. Normally distributed variables are presented as mean ± standard deviation, and non-normally distributed variables are presented as median with interquartile range. Continuous variables' between-group comparisons were performed using the Student's t-test or the Mann–Whitney U test, as appropriate. Categorical variables were shown as counts and percentages, and between-group comparisons were performed using the chi-square test. For ordinal variables with more than two levels where the global test was significant, pairwise comparisons were performed with Bonferroni correction. Missing data were handled using the multiple imputation by chained equations (MICE) method [24]. Continuous

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variables were imputed using a Bayesian ridge regression estimator, binary variables using mode imputation with subsequent hard clipping to a valid range, and ordinal variables using median imputation with rounding and range constraint. Twenty imputation iterations were performed. Post-imputation physiological plausibility checks were applied to continuous variables.

Feature Selection, Logistic Regression, and Machine Learning Algorithms

For the PO, a multivariable logistic regression (MLR) model was developed using a predefined feature selection approach. Continuous predictors were standardized using z-score transformation truncated at ±3 standard deviations to reduce the influence of extreme values and enable direct comparison of odds ratios across variables [25]. Feature selection was performed using a predefined approach incorporating univariate screening, correlation analysis, and multicollinearity assessment. Variables were further reduced using a backward elimination approach guided by statistical and clinical considerations with a removal threshold of $p > 0.07$. Model calibration was assessed using the Hosmer–Lemeshow goodness-of-fit test. Discrimination was summarized using the area under the receiver operating characteristic curve (AUROC). Results are presented as odds ratios (OR) with 95% confidence intervals (CI). Two-tailed p-values < 0.05 were considered statistically significant. Due to the limited events-per-variable ratio (EPV 1.2) in the SO, SO was analyzed using MLR only and was not included in machine learning modeling; thus, machine learning models were developed for the PO only.

Four classifiers were evaluated: logistic regression, random forest, extreme gradient boosting (XGBoost) [26], and categorical boosting (CatBoost) [27]. Hyperparameter optimization was performed using randomized search cross-validation with 30 iterations and five-fold stratified cross-validation, optimizing for AUROC. Feature selection was performed through mutual information ranking on the training set [28]. This approach was adopted because pure data-driven selection using mutual information failed to retain clinically essential predictors in preliminary analyses, attributable to shared variance among correlated renal function markers reducing their individual marginal information scores. Model performance was evaluated using stratified five-fold cross-validation with out-of-fold (OOF) predictions aggregated across the full dataset. This approach avoids optimistic bias from test-set evaluation on a small cohort and produces smooth discrimination curves by utilizing the full sample [29]. Performance metrics included AUROC, average precision, recall, precision, and F1-score, reported as mean ± standard deviation across folds. Receiver operating characteristic, precision–recall, and decision curve analysis plots were generated from OOF predictions [30]. Model interpretability was assessed using SHapley Additive exPlanations (SHAP) [31]. Feature importance was visualized using summary bar plots and beeswarm plots restricted to the top-ranked features, with SHAP values centered at zero to facilitate comparison of direction and magnitude of predictor contributions.

Software

All analyses were conducted in Python 3.14.2. Data processing and statistical analyses used pandas, NumPy, SciPy, and statsmodels. Machine learning models were implemented using scikit-learn [32], XGBoost, and CatBoost. Imputation was performed using the IterativeImputer implementation in scikit-learn. Interpretability analyses used the SHAP library. Figures were generated using Matplotlib.

Ethics

Patients in the study were assigned an anonymous identification number to protect confidentiality. Processing of this data does not require informed consent due to the study's non-interventional design. The study complies with the principles outlined in the Declaration of Helsinki, and it was approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethical Board on 25.12.2024, decision number: 2024/010.99/11/23, and each participating center also provided institutional approval.

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Results

Study Population and Baseline Characteristics

1180 patients in the FINE-TURK cohort were evaluated for eligibility. Of these, 249 patients had missing baseline potassium, eGFR, and follow-up potassium data; 169 patients' baseline potassium levels were over 4.8 mEq/L; 9 patients' duration of RAASi use was less than 4 months; and 54 patients' duration of SGLT2 inhibitor use was less than 4 months. 699 patients were included in the final analysis. Of those 699 patients, 259 (37%) patients reached the PO, and 51 (7.2%) patients reached the SO. Figure 1 presents the flowchart of the study.

The median age was 61 years, and 55% of patients were male. 26% of the patients smoked, and 76.7% of the patients never consumed alcohol. Age, sex, smoking, and alcohol use were similar in the patients who reached the PO and the SO. However, lack of physical exercise was more common in patients who reached the PO group, while it was similar in those who reached the SO group. SBP was similar between the patients who reached the PO and the SO. BMI was lower in the PO, but similar in the patients who reached the SO. Patients who reached the PO had a longer duration of T2DM and had more frequent DRP. Patients who reached the SO had a longer duration of T2DM as well and had a higher frequency of CAD and HF. Other comorbidities were similar between the patients who reached the PO and the SO.

In terms of contemporary CRM medications, all medications, as well as the finerenone dose, SGLT2 inhibitor, and RAAS inhibitor durations, were similar between the patients who reached the PO and the SO. Regarding traditional CRM medications, metformin, thiazide, and statin use were higher in the patients who did not reach the PO. DPP-4 inhibitor and loop diuretic use were higher in the patients who reached the SO. Other traditional CRM medications were similar in the patients of the PO and the SO groups.

In the patients who reached the PO, eGFR was lower (48.0 [37.5–65.0] vs. 56.5 [44.0–83.2], $p < 0.001$), and the baseline potassium level was higher (4.6 [4.3–4.7], vs. 4.3 [4.1–4.6], $p < 0.001$). Also, serum albumin was lower, uric acid was higher, and hemoglobin was lower, with the other values being similar in the patients who reached the PO. Similarly, eGFR was lower (45.0 [33.0–55.0] vs. 55.0 [42.0–80.0], $p < 0.001$), and the baseline potassium was higher (4.6 [4.3–4.7] vs. 4.4 [4.2–4.6], $p = 0.001$) in the patients who reached the SO. Furthermore, serum albumin and hemoglobin levels were lower in the patients who reached the SO. However, differing from the patients who reached the PO, sodium was lower, HbA1c was higher, and uric acid was similar in the patients who reached the SO. Table 1 demonstrates the baseline characteristics of the patients, grouping them according to PO-based hyperkalemia and SO-based hyperkalemia

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Table 1. Baseline characteristics of the patients included in the study, with grouping according to the primary outcome and secondary outcome.

VARIABLE	TOTAL COHORT	PRIMARY OUTCOME			SECONDARY OUTCOME		
		K < 5.0 mEq/L	**K ≥ 5.0 mEq/L**	**P**	**K < 5.5 mEq/L**	**K ≥ 5.5 mEq/L**	**P**
Number of the patients	699	440 (62.9%)	259 (37.1%)		648 (92.7%)	51 (7.3%)	
Demographics							
Age (Years)	61.0 [53.0–69.0]	61.0 [54.0–69.0]	61.0 [53.0–70.0]	0.60	61.0 [53.0–69.0]	65.0 [55.0–71.0]	0.22
Sex (Male)	385 (55.1%)	242 (55.0%)	143 (55.2%)	1.00	359 (55.4%)	26 (51.0%)	0.64
Lifestyle							
Smoking	183 (26.2%)	120 (27.3%)	63 (24.3%)	0.44	175 (27.0%)	8 (15.7%)	0.11
Alcohol use							
Never	529 (75.7%)	334 (75.9%)	195 (75.3%)		486 (75.0%)	43 (84.3%)	
<1/month	52 (7.4%)	30 (6.8%)	22 (8.5%)		50 (7.7%)	2 (3.9%)	
1-2/month	49 (7.0%)	27 (6.1%)	22 (8.5%)	0.24	47 (7.3%)	2 (3.9%)	0.46
≥ 1/week	15 (2.1%)	12 (2.7%)	3 (1.2%)		15 (2.3%)	0 (0.0%)	
Almost daily	3 (0.4%)	3 (0.7%)	0 (0.0%)		3 (0.5%)	0 (0.0%)	
Physical activity							
0 days	278 (39.8%)	157 (35.7%)	121 (46.7%)		254 (39.2%)	24 (47.1%)	
1-2 days	200 (28.6%)	128 (29.1%)	72 (27.8%)	**0.018**	185 (28.5%)	15 (29.4%)	0.26
3-4 days	81 (11.6%)	61 (13.9%)	20 (7.7%)		79 (12.2%)	2 (3.9%)	
≥ 5 days	37 (5.3%)	22 (5.0%)	15 (5.8%)		33 (5.1%)	4 (7.8%)	
Physical Examination							
Systolic BP (mmHg)	130.0 [120.0–140.0]	130.0 [120.0–141.0]	130.0 [120.0–140.0]	0.78	130.0 [121.0–140.0]	130.0 [120.0–140.0]	0.23
Body mass index (kg/ m²)	29.4 [26.2–33.8]	30.0 [26.7–34.2]	28.4 [25.8–32.9]	**0.011**	29.4 [26.3–33.7]	28.4 [26.1–34.4]	0.529

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Comorbidities							
Hypertension	658 (94.1%)	413 (93.9%)	245 (94.6%)	0.82	609 (94.0%)	49 (96.1%)	0.76
Hypertension duration (months)	132.0 [75.2–180.0]	133.0 [84.0–180.0]	129.5 [60.0–185.5]	0.37	132.0 [77.2–180.0]	180.0 [71.5–240.0]	0.16
DM duration (months)	120.0 [72.0–190.5]	120.0 [72.0–180.0]	150.0 [84.0–215.0]	**0.003**	120.0 [72.0–180.0]	180.0 [96.0–240.0]	**0.006**
Coronary artery disease	227 (32.5%)	140 (31.8%)	87 (33.6%)	0.69	201 (31.0%)	26 (51.0%)	**0.006**
Stroke	48 (6.9%)	31 (7.1%)	17 (6.6%)	0.92	43 (6.7%)	5 (9.8%)	0.57
Diabetic retinopathy	286 (43.3%)	156 (37.5%)	130 (53.1%)	**<0.001**	261 (42.5%)	25 (53.2%)	0.20
Peripheral sensorineural neuropathy	50 (7.2%)	27 (6.2%)	23 (9.0%)	0.23	43 (6.7%)	7 (14.0%)	0.10
HF	95 (13.7%)	67 (15.3%)	28 (11.0%)	0.14	82 (12.7%)	13 (26.0%)	**0.016**
Ejection fraction of the patients with HF							
EF >50%	16 (2.2%)	12 (2.7%)	4 (1.5%)		15 (2.3%)	1 (1.9%)	
EF 40-50%	55 (7.9%)	38 (8.6%)	17 (6.6%)	0.90	46 (7.1%)	9 (17.6%)	0.57
EF <40%	24 (3.4%)	17 (3.9%)	7 (2.7%)		21 (3.2%)	3 (5.9%)	
Contemporary Cardio-Renal-Metabolic Medications							
Finerenone dose (20mg)	118 (16.9%)	69 (15.7%)	49 (18.9%)	0.318	109 (16.8%)	9 (17.6%)	0.9
SGLT-2 inhibitor	622 (89.0%)	391 (88.9%)	231 (89.2%)	0.99	578 (89.2%)	44 (86.3%)	0.68
SGLT-2 inhibitor duration (months)	14.0 [6.0–30.0]	15.0 [6.0–30.0]	12.0 [7.0–26.0]	0.29	14.0 [6.0–28.0]	20.0 [12.0–36.0]	0.18
ACE inhibitor	316 (45.7%)	196 (45.0%)	120 (46.9%)	0.68	296 (46.2%)	20 (39.2%)	0.41
ARB	331 (47.6%)	216 (49.4%)	115 (44.6%)	0.25	306 (47.5%)	25 (49.0%)	0.95
Maximal RAAS blockade	418 (65.6%)	256 (63.5%)	162 (69.2%)	0.17	394 (66.6%)	24 (53.3%)	0.10
RAAS duration (months)	96.0 [36.0–144.0]	96.0 [36.0–143.5]	72.0 [32.5–146.0]	0.38	96.0 [36.0–144.0]	60.0 [22.2–127.8]	0.28
GLP-1 receptor agonist	40 (5.7%)	31 (7.0%)	9 (3.5%)	0.07	40 (6.2%)	0 (0.0%)	0.13

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DPP-4 inhibitor	357 (51.1%)	214 (48.7%)	143 (55.2%)	0.12	323 (49.9%)	34 (66.7%)	**0.031**
Traditional Cardio-Renal-Metabolic Medications							
Insulin	300 (42.9%)	177 (40.2%)	123 (47.5%)	0.07	272 (42.0%)	28 (54.9%)	0.1
Metformin	358 (51.2%)	242 (55.0%)	116 (44.8%)	**0.011**	336 (51.9%)	22 (43.1%)	0.29
Sulfonylurea	66 (9.5%)	43 (9.8%)	23 (8.9%)	0.79	64 (9.9%)	2 (3.9%)	0.25
Calcium channel blocker	338 (48.6%)	217 (49.7%)	121 (46.9%)	0.53	308 (47.8%)	30 (58.8%)	0.17
Beta-blocker	301 (43.4%)	196 (45.1%)	105 (40.7%)	0.3	277 (43.1%)	24 (47.1%)	0.69
Alpha-blocker	74 (10.7%)	47 (10.8%)	27 (10.5%)	1.0	68 (10.6%)	6 (11.8%)	0.98
Thiazide	293 (42.2%)	200 (45.9%)	93 (36.0%)	**0.014**	274 (42.6%)	19 (37.3%)	0.55
Loop diuretics	102 (14.7%)	66 (15.2%)	36 (14.0%)	0.74	88 (13.7%)	14 (27.5%)	**0.014**
Any anti-hypertensive	682 (97.8%)	428 (97.5%)	254 (98.4%)	0.57	632 (97.8%)	50 (98.0%)	1.00
Statin	443 (63.6%)	306 (69.9%)	137 (52.9%)	**<0.001**	410 (63.5%)	33 (64.7%)	0.98
Baseline Laboratory							
Potassium (mEq/L)	4.4 [4.2–4.7]	4.3 [4.1–4.6]	4.6 [4.3–4.7]	**<0.001**	4.4 [4.2–4.6]	4.6 [4.3–4.7]	**0.001**
eGFR (mL/min/1.73m²)	54.0 [41.5–78.5]	56.5 [44.0–83.2]	48.0 [37.5–65.0]	**<0.001**	55.0 [42.0–80.0]	45.0 [33.0–55.0]	**<0.001**
Urine albumin (mg/day)	649.5 [259.5–1446.8]	614.0 [226.0–1399.0]	719.0 [300.0–1512.0]	0.10	648.0 [242.0–1435.0]	669.5 [354.5–1645.0]	0.37
Sodium (mEq/L)	139.0 [138.0–141.0]	139.0 [138.0–141.0]	139.0 [137.0–141.0]	0.14	139.0 [138.0–141.0]	138.0 [136.0–139.0]	**0.001**
Serum albumin (g/dL)	4.2 [4.0–4.5]	4.3 [4.0–4.5]	4.1 [3.9–4.4]	**<0.001**	4.2 [4.0–4.5]	4.1 [3.8–4.3]	**0.005**
Uric acid (mg/dL)	6.1 [5.2–7.1]	6.0 [5.0–7.0]	6.5 [5.6–7.3]	**<0.001**	6.1 [5.2–7.1]	6.1 [5.3–7.4]	0.35
HbA1c (%)	7.2 [6.5–8.5]	7.2 [6.5–8.6]	7.3 [6.6–8.5]	0.82	7.2 [6.5–8.5]	7.7 [7.1–8.8]	**0.012**
Hemoglobin (g/dL)	13.5 ± 1.9	13.7 ± 1.9	13.1 ± 1.8	**<0.001**	13.5 ± 1.9	12.5 ± 1.8	**<0.001**

ACE: Angiotensin converting enzyme, ARB: Angiotensin receptor blocker, BP: Blood pressure, DM: Diabetes mellitus, DPP-4: Dipeptidyl peptidase-4, EF: Ejection fraction, eGFR: Estimated glomerular filtration rate, GLP-1: Glucagon-like peptide-1, HbA1c: Glycated hemoglobin, HF: Heart failure, RAAS: Renin angiotensin aldosterone system, SGLT2: Sodium-glucose transporter-2. *p values with statistical significance are shown in bold.

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Factors Associated with Hyperkalemia

Conventional MLR demonstrated that the baseline potassium level showed the strongest association with PO, with an OR (95% CI) of 2.09 (1.72-2.55) ($p < 0.001$). The presence of DRP, longer diabetes duration, higher uric acid levels, lower albumin levels, lower eGFR, and lack of thiazide were factors associated with the PO as well, with lower ORs. Regarding the factors associated with the SO, the baseline potassium level was the most important determinant as well, with an OR (95% CI) of 1.66 (1.15-2.38) ($p = 0.006$). Lower sodium, hemoglobin, and eGFR levels were associated with the SO, with lower ORs. Figure 2 demonstrates the MLR of the PO and the SO.

SHAP analysis revealed a consistent hierarchy of feature contributions across all four classifiers. Baseline serum potassium and eGFR were the two dominant features in all four models, with higher baseline potassium and lower baseline eGFR values being associated with strongly positive SHAP contributions, confirming their primacy as factors associated with hyperkalemia. Serum albumin and hemoglobin showed negative SHAP contributions across all four models, suggesting that lower albumin and hemoglobin values were associated with hyperkalemia risk. Longer diabetes duration, lack of beta-blocker use, shorter SGLT2 inhibitor duration, and higher urinary albumin appeared consistently in the top features across models to suggest hyperkalemia risk, though with smaller effect magnitudes. Figure 3 and supplementary figure 1 demonstrate SHAP beeswarm plots and SHAP bars, respectively.

Machine Learning Model Performance

Discrimination was moderate and broadly consistent across all four models. Logistic regression achieved the highest AUROC (0.713 ± 0.040), followed by random forest (0.709 ± 0.033), CatBoost (0.705 ± 0.043), and XGBoost (0.704 ± 0.027). Average precision scores were similarly comparable, ranging from 0.580 to 0.603, against a baseline prevalence of 0.37. Decision curve analysis demonstrated that all four models provided positive net benefit over the treat-all and treat-none strategies across a clinically plausible threshold range of approximately 0.20 to 0.55. At lower thresholds (0.20–0.40), all models outperformed treat-all, with tree-based classifiers maintaining a net benefit advantage over logistic regression at thresholds above 0.40. Performance profiles diverged considerably across classifiers when examining sensitivity and precision trade-offs. Logistic regression demonstrated the highest recall (0.695 ± 0.047) at the cost of lower precision (0.503 ± 0.041), yielding an F1-score of 0.581 ± 0.020. Random forest showed the inverse pattern, achieving the highest precision (0.670 ± 0.107) but substantially lower recall (0.278 ± 0.017) and the lowest F1-score (0.391 ± 0.029), indicating a conservative classification tendency. XGBoost and CatBoost occupied intermediate positions, with recalls of 0.433 ± 0.060 and 0.383 ± 0.074 and F1-scores of 0.498 ± 0.050 and 0.467 ± 0.073, respectively. Cross-validation stability, assessed through fold-level metric distributions, was broadly acceptable across all models. AUROC deviations across folds were modest for random forest and XGBoost, while CatBoost showed somewhat wider variability in AUPRC and F1, reflecting sensitivity to fold composition in the presence of moderate class imbalance. Recall distributions were notably wider for tree-based models compared to logistic regression, consistent with the greater susceptibility of ensemble methods to threshold-dependent instability on smaller datasets. Figure 4 and supplementary figure 2 illustrate the performance metrics of the classifiers.

Discussion

In this real-world cohort, the incidence of clinically meaningful hyperkalemia with finerenone was comparable to that reported in clinical trials and baseline potassium and eGFR were consistently the strongest factors associated with hyperkalemia across both conventional and machine learning approaches, followed by diabetes duration, the presence of DRP, and a lack of thiazide diuretic use. Low albumin, sodium, and uric acid levels were also modestly associated with hyperkalemia risk. To

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our knowledge, this is the first study to identify factors associated with finerenone-associated hyperkalemia in real-world patients.

Medication side effects may differ from those encountered in clinical trials [33]. There were also concerns reported about whether real-world hyperkalemia might differ from that which is reported in clinical trials [18,19]. FIGARO-DKD and FIDELIO-DKD were the two phase 3 trials to evaluate the efficacy of finerenone in DKD and reported hyperkalemia ($K^+ > 5.5$mEq/L) incidence was 21.7% and 13.5%, respectively. However, only 7.3% of our cohort reached the SO. Even though the percentage of patients on maximal RAAS inhibition was significantly higher (65.6%) than those on FIGARO-DKD (39.1% for RAAS inhibitors) and FIDELIO-DKD (21.4% and 56.6% for ACE inhibitors and ARBs, respectively) trials, we report lower hyperkalemia ($K^+ > 5.5$mEq/L) rates. This difference may emanate from several factors. Firstly, SGLT2 inhibitor use was very low, with 8.5% and 4.4% in these trials, compared to our cohort's SGLT2 inhibitor use of 89%. Previous studies with RAAS inhibitors, as well as the post hoc safety analysis of FIDELIO-DKD, have demonstrated that SGLT2 inhibitors reduce the hyperkalemic effect of RAAS inhibitors and finerenone [17,34]. Also, a recent study that incorporated the SGLT2 inhibitor empagliflozin and finerenone illustrated that hyperkalemia ($K^+ > 5.5$mEq/L) frequency was 15.6% in the finerenone plus empagliflozin group and 18.6% in the finerenone group [35], indicating the potassium-lowering effect of SGLT2 inhibitors. Secondly, thiazides are known for their kaliuretic effect and were shown to be associated with lower RAAS inhibitor-associated hyperkalemia in an observational study [34] and lower hyperkalemia risk in the post hoc safety analysis [17]. Our findings are in parallel with previous findings that thiazide use is associated with lower hyperkalemia risk, suggesting a potential modulatory role for thiazide diuretics in the contemporary cardio-renal-metabolic armamentarium by enabling the use of RAAS inhibitors and finerenone; however, this warrants prospective evaluation. Since 42.2% of our cohort were on thiazides and only 24.7% were using thiazides in FIGARO-DKD and FIDELIO-DKD studies, this major difference may explain the different hyperkalemia incidences between our real-world study and clinical trials. However, our findings should be interpreted cautiously due to potential residual confounding, such as patients on thiazides are likely to have less advanced CKD. Finally, the mean finerenone dose in our cohort was 11.6 mg, which is low compared to 17.5 and 15.1 mg in FIGARO-DKD and FIDELIO-DKD trials, respectively. An almost 50% dose difference may have resulted in a lower observed hyperkalemia incidence.

Machine learning algorithms have applications from optimizing drug selection to predicting therapeutic efficacy and adverse effects [34,36–39]. Various models have different performance metrics and resulting applications [38]. Similar to the algorithms that we applied, a recent systematic review has demonstrated that logistic regression, random forest, and XGBoost were the three most commonly used algorithms for drug adverse event prediction [37]. The concordance of feature rankings across algorithms in our study strengthens confidence in the clinical plausibility of these findings, since consistent identification of the same features across distinct algorithms reduces the likelihood of model-specific artifacts. Our study has demonstrated that logistic regression has negative net benefit beyond approximately 0.55, reflecting its higher sensitivity and correspondingly lower positive predictive value at elevated decision thresholds. However, in a clinical screening context where missing a hyperkalemia event carries greater consequence than a false positive, the higher sensitivity of logistic regression is arguably preferable despite its lower precision. For clinical applications prioritizing the detection of all at-risk patients (e.g., intensified monitoring protocols), logistic regression's higher recall profile remains advantageous.

Our study has several strengths. This study was conducted using the latest and novel machine learning algorithms, which have the potential to uncover features that may not be captured via conventional statistical methods. Secondly, baseline characteristics, inclusion and exclusion criteria of our cohort resulted in similar cohort with clinical trials in terms of age, gender, baseline potassium and eGFR, HbA1c, BMI, systolic blood pressure, urinary albumin, medical history, diabetes duration, and baseline medications except for the SGLT2 inhibitors and thiazides. This similarity has enabled our data to be directly comparable with clinical trial data and enable more robust interpretation.

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We acknowledge our limitations as well. Firstly, we only report potassium data up to the third month; however, hyperkalemia may occur even after the first few months. Secondly, baseline potassium-binder use data were not available. Thirdly, only 16.9% of the patients in our cohort were on a 20 mg dose. Although statistical analysis did not reveal finerenone dose to be associated with hyperkalemia, these statistics might be a false negative due to the low number of patients. Fourthly, the EPV ratio was limited for the secondary outcome, which may increase the risk of overfitting and instability in multivariable regression estimates. Although the EPV ratio was adequate for the primary outcome, the use of a multi-step feature selection strategy may still introduce a risk of overfitting. Although we applied a predefined feature selection approach to limit model complexity, consistency of key features across multiple machine learning algorithms was interpreted as supportive evidence of stability rather than formal validation, providing partial reassurance regarding the robustness and clinical plausibility of the findings. The results should be considered exploratory and hypothesis-generating, external validation in independent cohorts is warranted, and future studies using larger datasets and penalized regression approaches are needed to further validate these associations. Finally, due to the observational design of the study, residual confounding cannot be excluded despite adjustment for multiple clinical variables.

In conclusion, the finerenone-associated hyperkalemia is similar to that reported in clinical trials and may be even lower due, in part, to the widespread adaptation of SGLT2 inhibitors. Consistent with clinical trial results and in parallel with DKD pathophysiology, factors associated with finerenone-associated hyperkalemia were lower eGFR, higher baseline potassium, longer diabetes duration, presence of diabetic retinopathy and lack of thiazide diuretic use.

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