Original Article

JOURNAL OF MULTIMORBIDITY & COMORBIDITY

Journal of Multimorbidity and Comorbidity
Volume 12: 1–13

DOI: 10.1177/26335565221098832
journals.sagepub.com/home/cob
SAGE

Multiple comorbid conditions and healthcare resource utilization among adult patients with hyperkalemia: A retrospective observational cohort study using association rule mining

Dingwei Dai[1], Ajay Sharma[1], Paula J Alvarez[2] and Steven D Woods[2]

Abstract

Objectives: To estimate the prevalence of specific comorbid conditions (CCs) and multiple comorbid conditions (MCCs) among adult patients with hyperkalemia and examine the associations between MCCs and healthcare resource utilization (HRU) and costs.

Methods: This retrospective observational cohort study was conducted using a large administrative claims database. We identified patients with hyperkalemia (ICD-10-CM: E87.5; or serum potassium >5.0 mEq/L; or NDC codes for either patiromer or sodium polystyrene sulfonate) during the study period (1/1/2016–6/30/2019). The earliest service/claim date with evidence of hyperkalemia was identified as index date. Qualified patients had ≥12 months of enrolment before and after index date, ≥18 years of age. Comorbid conditions were assessed using all data within 12 months prior to the index date. Healthcare resource utilization and costs were estimated using all data within 12 months after the index date. Association rule mining was applied to identify MCCs. Generalized linear models were used to examine the associations between MCCs and HRU and costs.

Results: Of 22,154 patients with hyperkalemia, 94% had ≥3 CCs. The most common individual CCs were chronic kidney disease (CKD, 85%), hypertension (HTN, 83%), hyperlipidemia (HLD, 81%), and diabetes mellitus (DM, 47%). The most common dyad combination of CCs was CKD+HTN (71%). The most common triad combination was CKD+HTN+HLD (62%). The most common quartet combination was CKD+HTN+HLD+DM (36%). The increased number of CCs were significantly associated with increased ED visits, length of hospital stays, and total healthcare costs (all p-value < 0.0001).

Conclusions: MCCs are very prevalent among patients with hyperkalemia and are strongly associated with HRU and costs.

Keywords

hyperkalemia, chronic kidney disease, multimorbidity, resource utilization, association rule mining

Received 11 November 2021; accepted: 19 April 2022

Introduction

Hyperkalemia, defined as an elevated serum potassium concentration (>5.0 mmol/L), is a potentially life-threatening electrolyte abnormality.[1,2] Hyperkalemia is

[1]CVS Health Clinical Trial Services LLC, Woonsocket, RI, USA
[2]Managed Care Health Outcomes, Vifor Pharma Inc., Redwood City, CA, USA

Corresponding author:
Dingwei Dai Real World Evidence and Epidemiology CVS Health Clinical Trial Services LLC 1425 Union Meeting Road Blue Bell, PA 19422, USA.
Email: Dingwei.Dai@cvshealth.com

primarily caused by a reduction in the renal excretion of potassium or an intracellular-to-extracellular shift in potassium and increased serum potassium levels that results from various clinical conditions such as chronic kidney disease (CKD), congestive heart failure (CHF), diabetes mellitus (DM), and hypertension (HTN).[2–5] Concomitant diseases affecting the ability to excrete potassium, such as CKD and DM with nephropathy affecting renal parenchyma, further exacerbate hyperkalemia.[4] In addition, the use of renin-angiotensin-aldosterone system (RAAS) inhibitors, such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, mineralocorticoid receptor antagonists, and direct renin inhibitors, has been shown to further increase the serum potassium levels and exacerbate the risk of hyperkalemia.[6–8] At present, RAAS inhibitors are recommended by clinical practice guidelines for several conditions, such as CKD,[9] CHF,[10] DM, and HTN.[11] Thus, these medications are widely used in circumstances that predispose patients to hyperkalemia.

There is currently a lack of clinical guidance related to the treatment of chronic hyperkalemia. The only existing specific medications for patients with hyperkalemia are sodium polystyrene sulfonate (SPS), patiromer and sodium zirconium cyclosilicate.[4,12–14] Comorbid conditions (CCs) such as CKD, CHF, HTN, and DM are commonly seen in conjunction with hyperkalemia,[15] and the appropriate evaluation and treatment of these CCs can lead to more effective disease management and improve patient outcomes.[7,9] Although the prevalence of some individual CCs in patients with hyperkalemia has been reported in the literature,[15,16] these CCs do not occur in isolation; clinicians and healthcare providers are often faced with a constellation of multiple CCs (MCCs) impacting treatment options and disease management.

It is estimated that 3.7 million US adults had hyperkalemia in 2014, an annual prevalence of 1.55%, and this prevalence rate has increased since 2010.[15] A study in Canada showed the incidence of hyperkalemia to occur in 2.6% of emergency department (ED) visits and 3.5% of hospital admissions.[17] Studies have shown that hyperkalemia is associated with an increased risk for mortality[18–21] and an increased use of healthcare resources including hospitalizations,[16,21,22] especially among elderly patients and patients with CCs. A recent study showed that hyperkalemia was associated with an increased hospitalization rate and mortality in patients with CKD who were not undergoing dialysis.[2] One study that utilized real-world claims data found that hyperkalemia and suboptimal dosing of RAAS inhibitors were associated with a median increase in outpatient office visits as well as increased overall medical costs among patients with CKD and/or CHF.[23] Although the causes for higher mortality and cost are not entirely clear, accumulated real-world evidence supports that MCCs may contribute to increased mortality and cost in patients with hyperkalemia.[16,18,21–23] Although some studies have examined the prevalence of individual CCs in hyperkalemia, there are no published data about MCCs in this population. The objectives of the current study were to quantify the prevalence of specific CCs and MCCs among patients with hyperkalemia and examine the associations between MCCs and healthcare resource utilization (HRU) and costs.

Methods

Study design and data source

We conducted a retrospective observational cohort study of adult patients with hyperkalemia using Aetna's administrative claims data from January 1, 2016, to June 30, 2019 (study period). The database includes over 20 million Aetna members and contains patient enrolment and inpatient and outpatient medical and pharmacy claims for fully insured commercial health plan and Medicare Advantage members. Records were linked for each patient using a unique patient identifier. The Aetna laboratory database clinically enriches the medical and prescription drug data for a subset of patients in the Aetna Enterprise Data Warehouse by linking patients' claims data with predominately outpatient laboratory test results. All data handling complied with federal and state requirements; and the privacy and security of individually identifiable personal health information, required by Health Insurance Portability and Accountability Act (HIPAA) Standards, were preserved. As this non-experimental study did not require direct patient identification, a Limited Data Set defined by the HIPAA Privacy Rule was used. The study was approved by an independent institutional review board before initiation.

Patient selection

Patients 18 years of age or older with hyperkalemia were identified between January 1, 2017 and June 30, 2018 (index period, Figure 1). A patient was considered to have hyperkalemia if he/she met at least one of the following criteria: (1) >2 serum potassium >5.0 mmol/L on separate dates; (2) >2 claims with a primary or secondary hyperkalemia diagnosis (International Classification of Diseases, Tenth Revision, Clinical Modification [(ICD-10-CM: E87.5]); (3) 1 claim with a primary or secondary hyperkalemia diagnosis (E87.5) and 1 serum potassium >5.0 mmol/L; (4) ≥1 dispensed prescription for SPS or patiromer (SPS and patiromer were the only medications approved by the US Food and Drug Administration for treatment of hyperkalemia before 2018). The index date for each patient was defined as the earliest service/claim date with evidence of hyperkalemia during the index period. Patients with hyperkalemia were eligible for

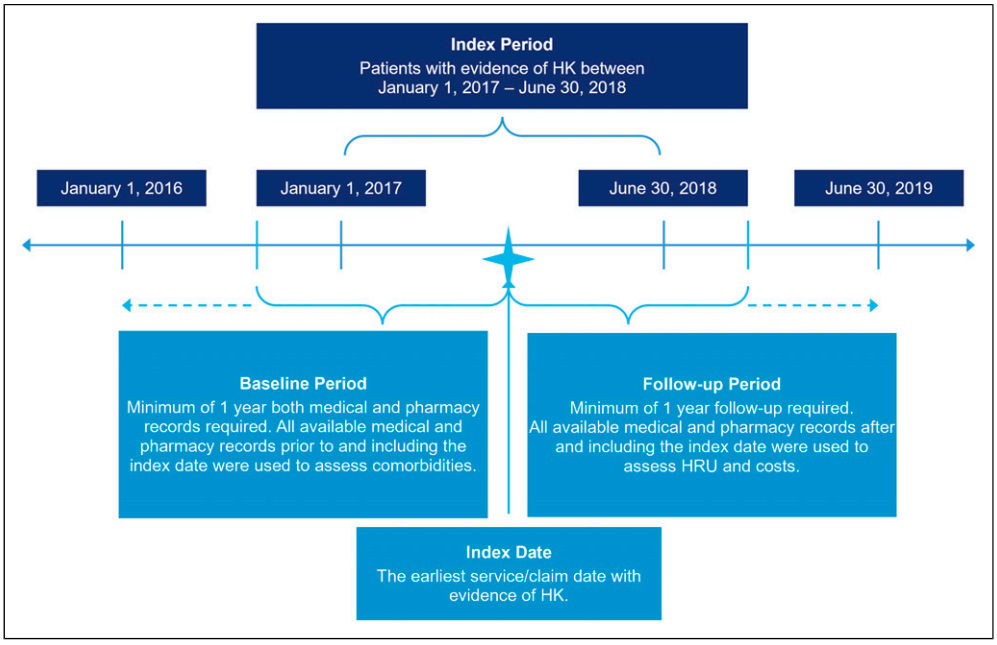

Figure 1. Study design.

inclusion in the study if they had an Aetna fully insured commercial health plan or Medicare Advantage with medical and pharmacy health insurance benefits for at least 12 months prior to the index date (baseline period) and 12 months after the index date (follow-up period). Patients who enrolled in Aetna's Compassionate Care program or hospice care anytime in the study period were excluded.

Identification of comorbid conditions

In patients with hyperkalemia, CC refers to one or more conditions that occur together with hyperkalemia.[24,25] Presence of CCs was assessed using all available data (any positions in inpatient and outpatient claims) prior to and including the index date (Figure 1). The following CCs were classified and evaluated in this study: atrial fibrillation (AFF), HIV/AIDS (AID), anxiety (ANX), asthma (AST), bipolar disorder (BIP), malignant cancer (CAN), cerebrovascular disease (CBD), congenital heart disease (CHD), CHF, cholelithiasis/cholecystitis (CHO), CKD, chronic obstructive pulmonary disease (COP), Crohn's disease (CRO), chronic thyroid disorders (CTD), dementia (DEM), depression (DEP), DM, diverticular disease (DTD), epilepsy (EPL), fibromyalgia (FIB), glaucoma (GLC), hypercoagulable syndrome (HCG), hepatitis (HEP), hyperlipidemia (HLD), hypertension (HTN), iron deficiency anemia (IDA), ischemic heart disease (IHD), kidney stones (KST), low back pain (LBP), multiple sclerosis (MSS), metabolic syndrome (MSX), nonspecific gastritis/dyspepsia (NGD), obesity (OBE), osteoporosis (OSP), osteoarthritis (OST), pancreatitis (PAN), Parkinson's disease (PAR), psychoses (PSY), peptic ulcer disease (PUD), peripheral vascular disease (PVD), rheumatoid arthritis (RHA), sickle cell anemia (SCA), substance related disorders (SDO), systemic lupus erythematosus (SLE), and ventricular arrhythmia (VNA). Chronic kidney disease was defined based on the presence of an ICD-10-CM diagnosis code (N18.1–6) or an estimated glomerular filtration rate (eGFR) measure <90 mL/min/1.73m^2 using the most recent measurement prior to the index date. If not already estimated in the database, eGFR was calculated using the Modification of Diet in Renal Disease study equation. All other conditions were defined using previously described methods based on ICD-10-CM codes; all of the ICD-10-CM codes are listed in (Supplemental Table 1)[26] Association rule mining is sensitive to combinations of conditions of very high frequency with conditions of very low frequency. To avoid detecting spurious associations, we limited our analysis to these more common conditions.

Outcomes

The outcomes of interest in this study included the proportion of hyperkalemia patients with the top 10 most common CCs, number of CCs, common MCCs, ED visits, length of hospital stay, and total healthcare cost during the follow-up period. The length of hospital stay was estimated by summarizing all hospital stays in days. Total healthcare costs included costs for all outpatient, inpatient, ED, pharmacy, laboratory, radiology, operating room, supplies, and other ancillary services.

Statistical analysis

Medians (interquartile ranges) and count (percentages) were used to describe the distribution of continuous and categorical variables, respectively. Baseline characteristics were compared between age groups (<65, ≥65 years) using the Pearson x^2 test for categorical variables and Kruskal–Wallis test for continuous variables.

Network analysis was performed using Gephi version 0.9.2 network analysis and visualization software with ForceAtlas 2 layout and modularity determined using a resolution of 0.6.[27] We computed the condition specific MCCs by implementing association rule mining. Association rule mining, also called frequent pattern mining, is a well-established machine learning technique for discovering relationships between variables in large databases.[28] An Apriori algorithm is a method designed to efficiently identify association rules in a large database.[28,29] The Apriori algorithm "prunes" the search space of associations based on the basic downward closure property of frequency.[29] In our context, this means that if a certain combination of CCs is infrequent, then any larger CCs combination that builds upon the smaller infrequent one will also be infrequent, and therefore does not need to be considered. To describe the patterns of MCCs, we calculated the number of discrete CCs for each patient and computed each specific CC, two to five CC combinations prevalence rate. Analyses were conducted for the overall population, as well as by age groups. Wilcoxon rank sum tests (Mann–Whitney U tests) were used to compare the mean numbers of CCs between age groups. Pearson x^2 tests were used to compare the rates of specific CCs or combinations of 2–5 CCs between age groups.

The rates and 95% confidence intervals (CIs) of the ED visits were used to compare the differences among patients with different numbers of CCs. The means and 95% CIs of the length of stay and total healthcare costs were used to compare the differences among patients with different numbers of CCs. To assess the association of the number of CCs and each outcome measure ED visit, length of hospital stays, and total healthcare costs, we also performed multivariable regression models after adjusting for other potential contributors: gender, age, median household income quartile, geographic region (Northeast, Midwest, South, and West), rural-urban, and type of health insurance (commercial insurance and Medicare Advantage). Logistic regression model was used for ED visits (binary outcome). The distribution of healthcare cost is skewed to the right and the assumption of homoscedasticity is often violated; therefore, the generalized linear models with gamma distribution and log link function for maximum-likelihood estimation were used for length of hospital stay and total healthcare cost.

All data management and statistical analyses were conducted using SAS version 9.4 statistical software and SAS Enterprise Miner version 15.1 (SAS Institute Inc., Cary, NC, USA). All p values are two-sided, with $p < 0.05$ considered statistically significant.

Patient involvement

This research (which was based on deidentified patient records) was performed without direct patient involvement. There was no patient input in the study design, interpretation of the results or drafting of the manuscript.

Results

Patient characteristics

Table 1 displays the descriptive characteristics of the study population, overall and by age groups. Of the 22,154 eligible patients (Supplemental Figure 1), 52% were male and the median age was 72 years, 75.6% were age ≥65 years, 44.8% were in the southern United States, and 38.9% lived in rural areas and median household income was $56,206. Medicare patients made up 75.6% of the study population; the remaining 24.4% were commercial patients. Over 65% of patients were receiving RAAS inhibitor therapy. Among these RAAS inhibitor users, only 27% were using optimal dose and 62.8% had good adherence. Only 2.6% of patients had potassium binder therapy (SPS or patiromer). Patients in the age ≥65 years group were sicker, had more CCs (7.2 vs 5.6), higher RAAS inhibitor use (68.5% vs 53.0%), better RAAS inhibitor adherence (64.7% vs 55.2%) and slightly higher potassium binder use (2.9% vs 1.8%) than patients <65 years.

Multiple comorbid conditions were prevalent among patients with hyperkalemia

Supplemental Figure 2 shows the top 30 most common CCs in this cohort. The most common CCs are CKD (85.2%), HTN (83.3%), HLD (80.6%), and DM (47.2%). Figure 2 shows a network of the 45 CCs. This demonstrates graphically the complicated nature of interactions between CCs and the dominance of CKD, HTN and HLD in this cohort. Table 2 lists the prevalence of the top 10 most common individual CCs and the MCCs, up to 5 CCs combination, overall and by age groups. The most common dyad CC combinations were CKD-HTN (71.4%) and HTN-HLD (71.4%). The most common triad combinations were CKD-HTN-HLD (61.8%) and HTN-HLD-DM (40.9%). The most common quartet combinations were CKD-HTN-HLD-DM (36%) and CKD-HTN-HLD-NGD (26.1%). The most common 5-CC combinations were CKD-HTN-HLD-DM-NGD (15.5%) and CKD-HTN-HLD-DM-OBE (12.7%). Summary MCC data are shown in Figure 3(a) to (d); 76.6% of patients with hyperkalemia had five or more CCs, while only 1.7% had only one and 0.3% had no comorbidities (Table 1). The mean number of CCs of patients with hyperkalemia is 6.8 (mean ±

Table 1. Baseline demographic and clinical characteristics of patients with hyperkalemia by age groups

Characteristics	Overall (N = 22,154)	Age <65 Years (N = 5,409, 24.42%)	Age ≥65 Years (N = 16,745, 75.58%)	p-value
Age				<0.0001
Mean (SD)	71.02 (12.49)	53.82 (9.17)	76.58 (7.28)	
Median (IQR)	72 (65–80)	56 (50–61)	76 (71–82)	
Gender, n (%)				<0.0001
Male	11,490 (51.86)	3146 (58.16)	8344 (49.83)	
Female	10,664 (48.14)	2263 (41.84)	8401 (50.17)	
Geographic Region				<0.0001
Midwest	4720 (21.31)	668 (12.35)	4052 (24.20)	
Northeast	6261 (28.26)	1171 (21.65)	5090 (30.40)	
South	9933 (44.84)	2915 (53.89)	7018 (41.91)	
West	1240 (5.60)	655 (12.11)	585 (3.49)	
Urban-rural				<0.0001
Urban	6962 (31.43)	2089 (38.62)	4873 (29.10)	
Sub-urban	6564 (29.63)	1558 (28.80)	5006 (29.90)	
Rural	8628 (38.95)	1762 (32.58)	6866 (41.00)	
Median Household Income ($)				<0.0001
Median (IQR)	56,206 (44,805–72,948)	60,978 (46,421–80,571)	55,080 (44,324–71,060)	
Payers				<0.0001
Commercial insurance	5409 (24.42)	3721 (68.79)	0 (0)	
Medicare	16,745 (75.58)	1688 (31.21)	16,745 (100)	
RAASi use				
ACE inhibitors	9005 (40.65)	1906 (35.24)	7099 (42.39)	<0.0001
ARB	5358 (24.19)	943 (17.43)	4415 (26.37)	<0.0001
MRA	1897 (8.56)	355 (6.56)	1542 (9.21)	<0.0001
Other	17 (0.08)	0 (0.00)	17 (0.10)	0.0191
RAASi any	14,333 (64.70)	2868 (53.02)	11,465 (68.47)	<0.0001
Optimal RAASi dose	3837 (27.00)	721(25.35)	3116 (27.41)	0.0270
RAASi PDC ≥0.80	9002 (62.81)	1582 (55.16)	7420 (64.72)	<0.0001
Potassium binder use	575(2.60)	97 (1.79)	478 (2.85)	<0.0001
Number of comorbidities, mean (SD)	6.82 (3.05)	5.56 (3.12)	7.22 (2.91)	<0.0001
Hyperkalaemia only	58 (0.26)	38 (0.70)	20 (0.12)	
1 comorbidity	375 (1.69)	281 (5.20)	94 (0.56)	
2 comorbidities	894 (4.04)	499 (9.23)	395 (2.36)	
3 comorbidities	1545 (6.97)	677 (12.52)	868 (5.18)	
4 comorbidities	2317 (10.46)	766 (14.16)	1551 (9.26)	
5+ comorbidities	16,965 (76.58)	3148 (58.20)	13,817 (82.51)	

ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; IQR, interquartile range; MRA, mineralocorticoid receptor antagonist; PDC, proportion of days covered; RAASi, renin angiotensin aldosterone system inhibitor.

standard deviation: 6.8±3.1). Due to more comorbidity with aging, the mean number of CCs of patients aged 65 years or older (7.2±2.9) was significantly higher ($p < 0.0001$) than that of patients younger than 65 years (5.6±3.1).

Healthcare resource utilization and costs

Within 1 year of the follow-up period, over 86% of all patients with hyperkalemia had at least 1 outpatient visit, 36% had at least 1 ED visit, 35% had at least 1 inpatient admission, the average length of hospital stay was 4.42 days, and the average total healthcare cost was $31,251 (Supplemental Table 2).

Multiple comorbid conditions were associated with higher healthcare resource utilization and costs among patients with hyperkalemia

Figure 3(b) shows that the trend of the rates of ED visits was elevated with increased numbers of CCs for patients with

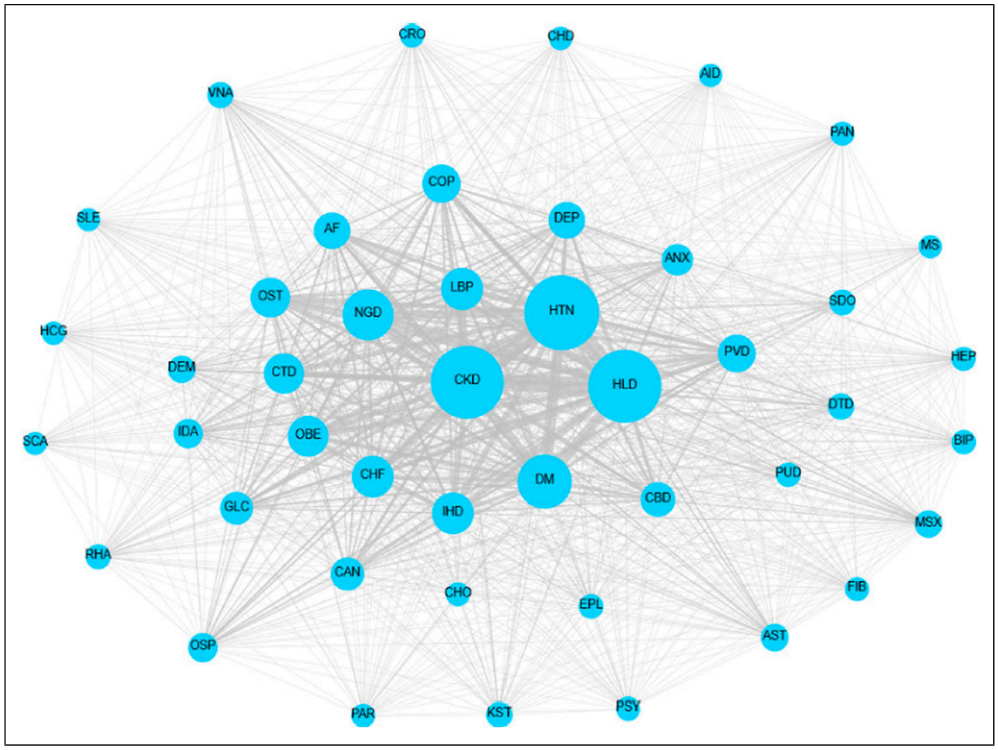

Figure 2. Network analyses of multimorbidity in patients with hyperkalemia. The nodes represent comorbidities; the lines linking the nodes represent the connection between two comorbidities. The size of node corresponds to the prevalence of the comorbidity. The thicker the line, the more frequently the two comorbidities coexisted. The network is dominated by CKD, HTN, and HLD. AF, atrial fibrillation; AID, acquired immunodeficiency syndrome; ANX, anxiety; AST, asthma; BIP, bipolar disorder; CAN, malignant cancer; CBD, cerebrovascular disease; CHD, congenital heart disease; CHF, congestive heart failure; CHO, cholelithiasis/cholecystitis; CKD, chronic kidney disease; COP, chronic obstructive pulmonary disease; CRO, Crohn's disease; CTD, chronic thyroid disorders; DEM, dementia; DEP, depression; DM, diabetes mellitus; DTD, diverticular disease; EPL, epilepsy; FIB, fibromyalgia; GLC, glaucoma; HCG, hypercoagulable syndrome; HEP, hepatitis; HLD, hyperlipidemia; HTN, hypertension; IDA, iron deficiency anemia; IHD, ischemic heart disease; KST, kidney stones; LBP, lower back pain; MSS, multiple sclerosis; MSX, metabolic syndrome; NGD, nonspecific gastritis/dyspepsia; OBE, obesity; OSP, osteoporosis; OST, osteoarthritis; PAN, pancreatitis; PAR, Parkinson's disease; PSY, psychosis; PUD, peptic ulcer disease; PVD, peripheral vascular disease; RHA, rheumatoid arthritis; SCA, sickle cell anemia; SDO, substance related disorders; SLE, systemic lupus erythematosus; VNA, ventricular arrhythmia.

hyperkalemia. After adjusting for other covariables including age, gender, region, rural or urban, household income, and type of health insurance, there was 20% odds for ED visits increased for patients with hyperkalemia with each additional CC (adjusted odds ratio [95% CI]: 1.20 [1.19–1.21], p <0.0001). Figure 3(c) shows that the trend of the means of hospital stay was increased with increased number of CCs for patients with hyperkalemia. After adjusting for other covariables including age, gender, region, rural or urban, household income and type of health insurance, there was a 5.8% increased length of hospital stay (in days) for patients with hyperkalemia with each additional CCs (p <0.0001). Figure 3(d) shows that the trend of the means of total healthcare costs was increased with increased number of CCs for patients with hyperkalemia. After adjusting for other covariables including age, gender, region, rural or urban, household income, and type of health insurance, there was a 7.8% increase in total healthcare costs for patients with hyperkalemia with each additional CC (p <0.0001). The detail multivariable regression results are presented in Supplemental Table 3.

Discussion

Using a large administrative healthcare claims database (augmented with laboratory data), through association rule mining, we found a wide spectrum of CCs and MCCs combinations among adult patients with hyperkalemia. Information on the prevalence of individual CCs is useful but lacks the complexity that physicians and healthcare providers face in routine clinical practice and disease management. Our study demonstrated that 94% of patients with hyperkalemia had at least three CCs, and >76% had 5 or more CCs. We also found that the burden of comorbidity

Table 2. Prevalence of the first 10 most CCs and MCCs in patients with hyperkalemia by age groups

Characteristics	Overall (N = 22,154)	Age <65 Years (n = 5409, 24.42%)	Age ≥65 Years (n = 16,745, 75.58%)	P-value
Comorbidity				
CKD	18,883 (85.24)	4719 (87.24)	14,164 (84.59)	<0.0001
HTN	18,460 (83.33)	3539 (65.43)	14,921 (89.11)	<0.0001
HLD	17,851 (80.58)	3662 (67.70)	14,189 (84.74)	<0.0001
DM	10,453 (47.18)	2300 (42.52)	8153 (48.69)	<0.0001
NGD	8515 (38.44)	1635 (30.23)	6880 (41.09)	<0.0001
IHD	5230 (23.61)	700 (12.94)	4530 (27.05)	<0.0001
LBP	5695 (25.71)	1301 (24.05)	4394 (26.24)	0.0014
CTD	5467 (24.68)	1036 (19.15)	4431 (26.46)	<0.0001
CHF	5031 (22.71)	701 (12.96)	4330 (25.86)	<0.0001
COP	4266 (19.26)	636 (11.76)	3630 (21.68)	<0.0001
2 comorbidities				
CKD-HTN	15,818 (71.40)	3091 (57.15)	12,727 (76.00)	<0.0001
HTN-HLD	15,811 (71.37)	2834 (52.39)	12,977 (77.50)	<0.0001
CKD-HLD	15,419 (69.60)	3250 (60.09)	12,169 (72.67)	<0.0001
HTN-DM	9755 (44.03)	1970 (36.42)	7785 (46.49)	<0.0001
HLD-DM	9596 (43.31)	2014 (37.23)	7582 (45.28)	<0.0001
CKD-DM	9125 (41.19)	2020 (37.25)	7105 (42.43)	<0.0001
HTN-NGD	7559 (34.12)	1253 (23.17)	6306 (37.66)	<0.0001
CKD-NGD	7272 (32.82)	1402 (25.92)	5870 (35.06)	<0.0001
HLD-NGD	7264 (32.79)	1262 (23.33)	6002 (35.84)	<0.0001
HTN-IHD	5053 (22.81)	659 (12.18)	4394 (26.24)	<0.0001
3 comorbidities				
CKD-HTN-HLD	13,691 (61.80)	2502 (46.26)	11,189 (66.82)	<0.0001
HTN-HLD-DM	9070 (40.94)	1774 (32.80)	7296 (43.57)	<0.0001
CKD-HTN-DM	8538 (38.54)	1729 (31.97)	6809 (40.66)	<0.0001
CKD-HLD-DM	8437 (38.08)	1792 (33.13)	6645 (39.68)	<0.0001
HTN-HLD-NGD	6672 (30.12)	1057 (19.54)	5615 (33.53)	<0.0001
CKD-HTN-NGD	6483 (29.26)	1072 (19.82)	5411 (32.31)	<0.0001
CKD-HLD-NGD	6278 (28.34)	1099 (20.32)	5179 (30.93)	<0.0001
HTN-HLD-IHD	4826 (21.78)	627 (11.59)	4199 (25.08)	<0.0001
HTN-HLD-OBE	4348 (19.77)	973 (17.99)	3375 (20.16)	0.0005
CKD-HTN-CHF	4228 (19.08)	577 (10.67)	3651 (21.80)	<0.0001
4 comorbidities				
CKD-HTN-HLD-DM	7985 (36.04)	1575 (29.12)	6410 (38.28)	<0.0001
CKD-HTN-HLD-NGD	5780 (26.09)	915 (16.92)	4865 (29.05)	<0.0001
CKD-HTN-HLD-IHD	4190 (18.91)	546 (10.09)	3644 (21.76)	<0.0001
CKD-HTN-HLD-OBE	3877 (17.50)	874 (16.16)	3003 (17.93)	0.0028
HTN-HLD-DM-NGD	3891 (17.56)	694 (12.83)	3197 (19.09)	<0.0001
CKD-HTN-HLD-CHF	3823 (17.26)	496 (9.17)	3327 (19.87)	<0.0001
CKD-HTN-HLD-LBP	3675 (16.59)	655 (12.11)	3020 (18.04)	<0.0001
CKD-HTN-DM-NGD	3623 (16.35)	649 (12.00)	2974 (17.76)	<0.0001
CKD-HLD-DM-NGD	3537 (15.97)	650 (12.02)	2887 (17.24)	<0.0001
CKD-HTN-DM-CHF	2547 (11.47)	404 (7.47)	2137 (12.76)	<0.0001
5 comorbidities				
CKD-HTN-HLD-DM-NGD	3429 (15.48)	606 (11.20)	2823 (16.86)	<0.0001
CKD-HTN-HLD-DM-OBE	2807 (12.67)	667 (12.33)	2140 (12.78)	0.3974

(continued)

Table 2. (continued)

Characteristics	Overall (N = 22,154)	Age <65 Years (n = 5409, 24.42%)	Age ≥65 Years (n = 16,745, 75.58%)	P-value
CKD-HTN-HLD-DM-IHD	2588 (11.68)	379 (7.01)	2209 (13.19)	<0.0001
CKD-HTN-HLD-DM-CHF	2414 (10.90)	368 (6.80)	2046 (12.22)	<0.0001
CKD-HTN-HLD-IHD-CHF	2156 (9.73)	260 (4.81)	1896 (11.32)	<0.0001
CKD-HTN-HLD-DM-LBP	2116 (9.55)	428 (7.91)	1688 (10.08)	<0.0001
CKD-HTN-HLD-IHD-NGD	2111 (9.53)	251 (4.64)	1860 (11.11)	<0.0001
CKD-HTN-HLD-DM-CTD	2020 (9.12)	313 (5.79)	1707 (10.19)	<0.0001
CKD-HTN-HLD-NGD-LBP	1973 (8.91)	324 (5.99)	1649 (9.85)	<0.0001
CKD-HTN-HLD-NGD-CHF	1928 (8.70)	251 (4.64)	1677 (10.01)	<0.0001

CC, comorbid condition; CHF, congestive heart failure; CKD, chronic kidney disease; CTD, chronic thyroid disease; COP; chronic obstructive pulmonary disease; DM, diabetes mellitus; HLD, hyperlipidemia; HTN, hypertension; IHD, ischemic heart disease; LBP, low back pain; MCC, multiple comorbid condition; NGD, nonspecific gastritis/dyspepsia; OBE, obesity

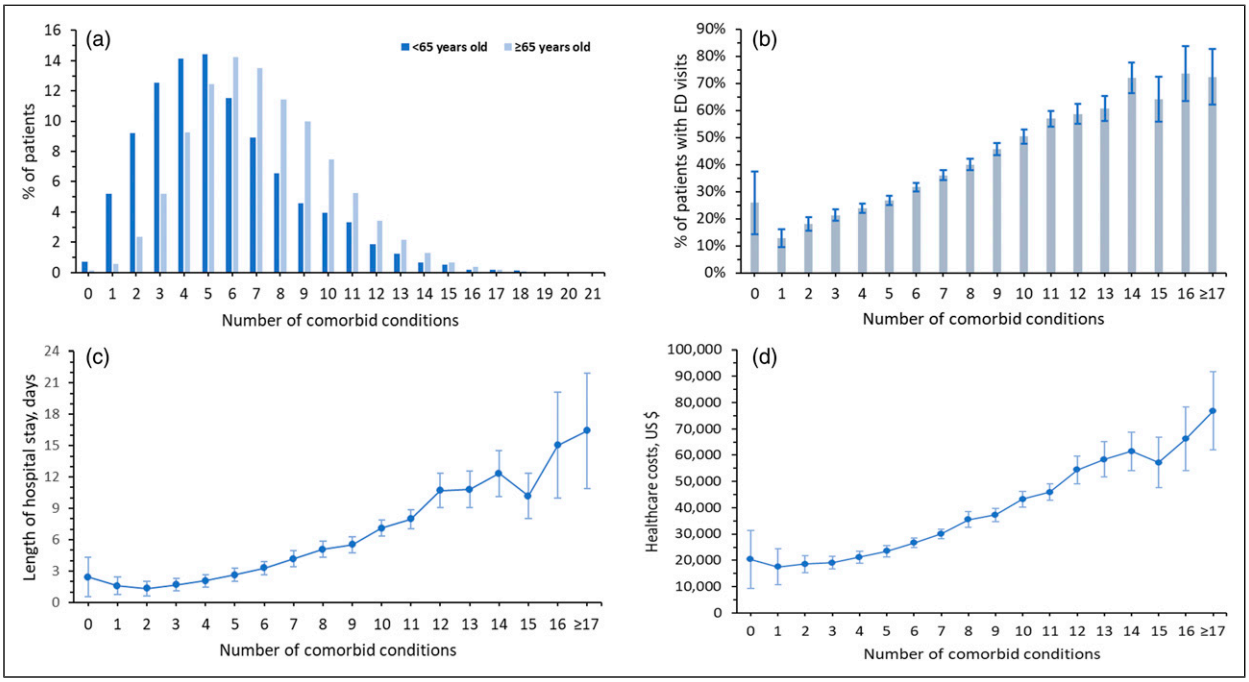

Figure 3. Number of CCs and their associations with HRU and total healthcare costs. (A) The prevalence of the number of CCs in adult patients with hyperkalemia by age groups. (B) The proportion of hyperkalemia patients with ED visits increased with increased number of CCs for patients with hyperkalemia. The averages and 95% CIs of proportion of hyperkalemia patients with ED visits were used to compare the differences among hyperkalemia patients with different numbers of CCs. (C) The length of hospital stays increased with increased number of CCs for patients with hyperkalemia. The means and 95% CIs of length of hospital stay were used to compare the differences among hyperkalemia patients with different numbers of CCs. (D) Healthcare costs increased with increased number of CCs for patients with hyperkalemia. The means and 95% CIs of healthcare costs were used to compare the differences among hyperkalemia patients with different numbers of CCs. CC, comorbid condition; CI, confidence interval; ED, emergency department; HRU, healthcare resource utilization.

increases with advancing age in hyperkalemia patients. The most common CCs are CKD (85.2%), HTN (83.3%), HLD (80.6%) and DM (47.2%), but there was a huge amount of interplay among these conditions when MCCs were explored. The average number of CCs of patients with hyperkalemia is 7 in this cohort. The most common dyad CC combinations were CKD-HTN (71.4%) and HTN-HLD (71.4%). The most common triad combinations were CKD-

HTN-HLD (61.8%) and HTN-HLD-DM (40.9%). The most common quartet combinations were CKD-HTN-HLD-DM (36%) and CKD-HTN-HLD-NGD (26.1%). The most common 5-CC combinations were CKD-HTN-HLD-DM-NGD (15.5%) and CKD-HTN-HLD-DM-OBE (12.7%).

The presence of MCCs poses challenges in disease management, including selection of the appropriate hyperkalemia prevention and treatment strategies. The profiles of available therapeutic options for hyperkalemia are varied, and not all drug and therapeutic agents may be appropriate for a given patient based on the clinical profile and existing CCs. We found that CKD, HTN, DM and CHF are all in the top 10 most common CCs in adult patients with hyperkalemia, 38.5% with CKD-HTN-DM and 11.4% with CKD-HTN-DM-CHF. The progression of CKD is characterized by a maladaptive cycle of activation of the RAAS and deterioration of kidney function, with impaired ability to excrete many substances, including potassium.[30, 31] RAAS inhibitors have been shown to slow disease progression and reduce mortality in patients with CKD, CHF, and DM.[32–37] Current clinical practice guidelines recommend RAAS inhibitors as integral components in the management and treatment of patients with CKD,[38,39] CHF,[40] and HTN,[38,41,42] and patients with DM and comorbid HTN or renal impairment.[11,38] However, hyperkalemia can impair the cardiovascular effects of RAAS inhibitors and potassium-rich diets, as hyperkalemia frequently leads to the discontinuation of both.[43] Concerns related to the risk of hyperkalemia with the use of RAAS inhibitors have contributed to suboptimal dosing, discontinuation and avoidance of RAAS inhibitor use when clinically indicated.[44–46]As a result, there is a large gap between real-world clinical practice and guideline recommendations in the use of RAAS inhibitors.[47–50] Our recent study found that the presence of hyperkalemia and poor RAAS inhibitors adherence are significantly associated with progression of CKD.[51] The ideal goal should be the achievement of both (controlled hyperkalemia and optimal RAAS inhibitors therapy), and hence therapies that control hyperkalemia without the discontinuation of hyperkalemia-inducing but otherwise beneficial interventions such as RAAS inhibitors and heart-healthy diets.[52,53] Randomized trials have shown that the new potassium binders (patiromer and zirconium cyclosilicate) are effective hyperkalemia treatment options.[12,54,55] The use of these agents may allow for a less restrictive potassium diet and lower RAAS inhibitor discontinuation rates.[44,56] Long-term management of serum potassium level is needed in patients with CKD taking RAAS inhibitors to reduce recurrence of hyperkalemia. Weir and colleagues demonstrated that in patients with CKD and hyperkalemia who are receiving RAAS inhibitors, patiromer treatment was associated with a decrease in serum potassium levels and a reduction in the recurrence of hyperkalemia.[12] Whether control of hyperkalemia and continued use of RAAS inhibitors in CKD will improve long-term outcomes remains to be established.

Our previous analysis showed that optimal dosing of RAAS inhibitors was associated with decreased inpatient admissions, outpatient visits, length of hospital stay and overall medical costs among CKD patients.[57] These results are consistent with the findings of two other studies. Epstein and colleagues reported that patients receiving RAAS inhibitor therapies at maximum doses incurred lower total costs per patient compared with those who had been prescribed RAAS inhibitor therapies at sub-maximum doses.[47] Similarly, Polson and colleagues found that among patients treated with RAAS inhibitor therapies, optimal dosing was associated with higher pharmacy costs but lower overall healthcare costs. In the same study, in hyperkalemia patients with both CKD and CHF and receiving RAAS inhibitor therapy at an optimal dose, median overall healthcare costs were lower compared with patients who were receiving a suboptimal dose.[23]

Modern medical management of MCCs has resulted in escalating use of multiple medications and the emergence of the phenomenon of polypharmacy.[58] Hyperkalemia is most common in older individuals; in patients with CKD, HTN, CHF, or other cardiovascular comorbidities; and in those taking multiple medications, including RAAS inhibitor therapy.[59] Schmidt and colleagues reported that 80% of CKD patients were exposed to polypharmacy, and the median number of different medications taken per day was 8 (range 0–27). Beta blockers, angiotensin-converting enzyme inhibitors, and statins were most frequently used. Increasing CKD stage, age, DM, cardiovascular comorbidities and a history of smoking were significantly associated with the prevalence of polypharmacy.[60] Polypharmacy may pose a risk for adverse drug interactions, accidental overdosing, or medication nonadherence.[61,62] Hyperkalemia patients with MCCs may also have many healthcare providers; without proper coordination, this could lead to fragmented care, duplication of services, inappropriate medications or polypharmacy, and/or adverse drug–drug interactions.[63,64] Recent studies have shown that increasing numbers of CCs are associated with higher odds for anxiety or depression [65,66] and decrease the patient's health-related quality of life.[58,67,68]

Hyperkalemia is associated with substantial economic burden among US commercially insured and Medicare populations.[16,22,23] The numbers of CCs are significantly associated with ED visits, length of hospital stay, and total healthcare costs. In an observational study by Betts et al, patients with hyperkalemia had significantly higher HRU—including ED visits, outpatient visits, inpatient admissions, and total healthcare costs—compared with matched controls.[22]

HRU, such as ED visits and/or inpatient admissions, can dramatically increase total healthcare costs for patients with hyperkalemia. Healthcare cost and utilization product data reported a mean inpatient cost of $24,178 (in 2011 USD) per episode with an average length of stay of 3.2 days among patients admitted from EDs to hospitals for elevated potassium levels.[69] One recent study found that approximately one third to one half of total healthcare costs for patients with hyperkalemia are directly attributed to inpatient admissions.[15] To our knowledge, ours is the first analysis examining the association between HRU and the numbers of CCs in patients with hyperkalemia. Our results clearly suggest that the numbers of CCs are significantly associated with ED visits, length of hospital stay and total healthcare costs. In a meta-analysis of 55 studies of high-cost patient characteristics and HRU, Wammes et al pointed to a high prevalence of MCCs to explain high-cost patient HRU.[70] Therefore, it is essential to better understand the MCCs that can lead to high HRU for patients with hyperkalemia.

This study has several strengths that warrant consideration. First, the large sample sizes available allowed us to estimate the prevalence of specific CCs and MCCs and assess the associations between HRU and costs and the numbers of CCs in patients with hyperkalemia. Second, all available data including medical claims (ICD-10-CM), pharmacy claims (medication prescriptions), and laboratory results were used to identify hyperkalemia and CKD to avoid underestimating and insure case ascertainment. Third, we have used association rule mining, which has been widely used in marketing and business analytics but rarely applied to clinical and outcomes research previously, although a few similar approaches have been reported recently.[71,72] The strength of unsupervised data mining is the discovery of interesting information that could not be obtained from large databases through conventional statistical methods. However, there are several limitations that could affect interpretation of these results. First, this is a healthcare administrative claims data analysis; therefore, we may have underestimated MCC prevalence rates and other results. Second, there are no standard operational definitions for CCs that should be used in such studies,[73] so we included the top 45 most common CCs and excluded the rare conditions. Since classification of most CCs was based on ICD-10-CM codes alone, misclassification is likely. However, this approach is common in other studies of comorbidities.[15,22,23] Third, the purpose of association rule mining is to identify combinations of CCs that are interesting and worthy of further investigation, but without addressing statistical significance. Fourth, multivariable generalized linear regression models were applied to control observed confounding factors in this study; we may have missed some factors such as race and ethnicity, health-related lifestyle factors (such as smoking status, alcohol intake, physical activity, and BMI), and clinical parameters (such as optimal RAAS inhibitors therapy); due to the retrospective, observational study design using an administrative claims database, the analysis may be also affected by unobserved differences between patients. In addition, the study results may not be generalizable to the overall population, as well as to other countries, for a variety of reasons.

Conclusion

Multiple comorbid conditions are highly prevalent among adult patients with hyperkalemia, and the MCCs patterns vary considerably across patients and by age groups. MCCs are strongly associated with HRU and healthcare costs. Specific disease management strategies should be developed for hyperkalemia patients with specific MCCs combinations to improve clinical outcomes and reduce HRU and costs. Association rule mining offers a useful new way to evaluate the patterns of MCCs in clinical, and health economics and outcomes research.

Acknowledgments

This work was presented at the International Society for Pharmacoeconomics and Outcomes Research, Virtual Annual International Meeting, May 16–20, 2020. The poster abstract was published in Value in Health 2020;23(suppl 1):S377. DOI: https://doi.org/10.1016/j.jval.2020.04.1462. Editorial support was provided by Impact Communication Partners Inc.

Author contributions

DD was responsible for concept and study design, statistical analysis, and drafting of the manuscript. AS was responsible for clinical concept and study design. PJA and SDW were responsible for concept development, study design, and obtained funding. All authors fully contributed to the content of this manuscript, including meeting the four criteria of the Internal Committee of Medical Journal Editors. All authors had full access to all the data in the study and take full responsibility for the integrity of the work and the accuracy of the data analysis, from inception to published article.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was supported by the This study was sponsored by Vifor Pharma Inc (VP201501).

Disclosure

DD, and AS report employment by Clinical Trial Services, CVS Health Corp, New York, NY, which conducted research funded by Vifor Pharma, Inc. PJA and SDW report employment by Vifor Pharma Inc., and stock in Vifor Pharma, Glattbrugg, Switzerland. The authors report no other conflicts of interest in this work.

Data sharing statement

This analysis is based on a large sample from Aetna's administrative claims data. The authors' license for using these data precludes the sharing of raw data with third parties.

Patient consent

For publication Not required. This study involved the use of anonymised patient medical records, which contained no information that could reasonably be used to identify people.

Ethics approval

As this non-experimental study did not require direct patient identification, a Limited Data Set defined by the HIPAA Privacy Rule was used. No ethics approval was required.

ORCID iD

Dingwei Dai https://orcid.org/0000-0001-9385-0992

Supplemental Material

Supplemental material for this article is available online.

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