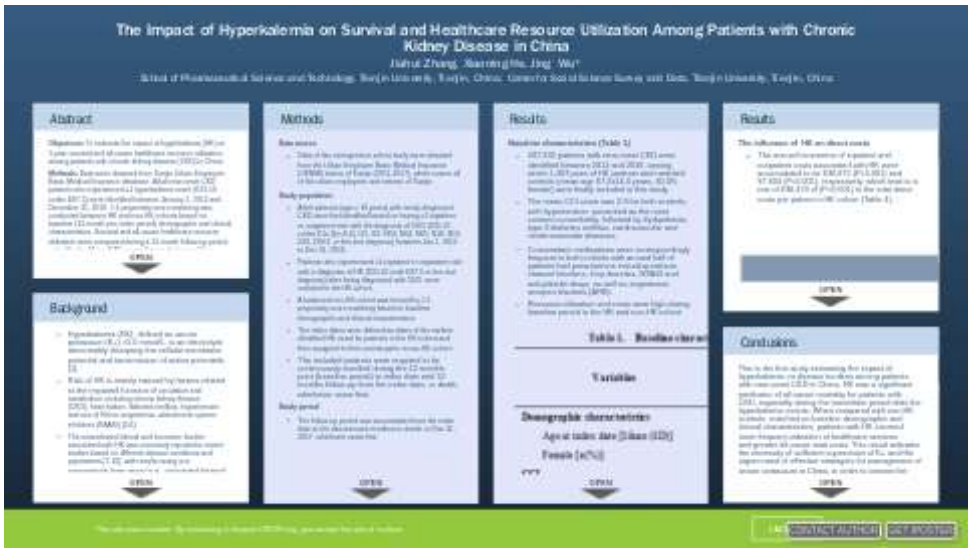
The Impact of Hyperkalemia on Survival and Healthcare Resource Utilization Among Patients with Chronic Kidney Disease in China



Jiahui Zhang, Xiaoning He, Jing Wu*

School of Pharmaceutical Science and Technology, Tianjin University, Tianjin, China; Center for Social Science Survey and Data, Tianjin University, Tianjin, China

PRESENTED AT:

ABSTRACT

Objectives: To estimate the impact of hyperkalemia (HK) on 1-year survival and all-cause healthcare resource utilization among patients with chronic kidney disease (CKD) in China.

Methods: Data were obtained from Tianjin Urban Employee Basic Medical Insurance database. Adult new-onset CKD patients who experienced ≥1 hyperkalemic event (ICD-10 codes E87.5) were identified between January 1, 2012 and December 31, 2016. 1:1 propensity score matching was conducted between HK and non-HK cohorts based on baseline (12-month pre-index period) demographic and clinical characteristics. Survival and all-cause healthcare resource utilization were compared during a 12-month follow-up period using Kaplan-Meier (KM) curves (Log-rank test and Cox proportional hazard model) and KM sample average method, respectively.

Results: Among 207,232 eligible CKD patients, 1,003 pairs of HK patients and matched controls were included (mean age 67.2 ± 14.3 years, 40.3% female). The 1-year all-cause mortality was much higher in the HK cohort than the non-HK cohort (36.4% vs. 8.3%, hazard ratio=5.39, P<0.001). The mean costs and number of healthcare services among HK patients in each follow-up month were significantly higher (P<0.05). An annual increase cost of ¥38,479 (¥59,210 vs. ¥20,732) was observed in HK cohort, largely due to the sharp increase in inpatient costs during the first month after HK events (¥22,204 vs. ¥1,032, P<0.001). Medication costs were the most important cost component for both cohorts (¥26,786 [45%] vs. ¥12,378[60%]). However, HK patients spent more on non-medication treatment (¥13,410 [23%] vs. ¥2,335[11%]) including nursing, monitoring, etc., primarily due to more emergency department visits, hospitalizations, and higher hospital tier visits. HK patients had more annual inpatient admissions (1.9 vs. 0.7) and length of stays (28.6 vs. 8.7), while number of outpatient visits (36.8 vs. 36.4) was similar.

Conclusions: In Chinese CKD patients, HK is associated with substantially increased mortality and healthcare resource utilization driven by the short period following the HK events.

BACKGROUND

- Hyperkalemia (HK), defined as serum potassium (K+) >5.0 mmol/L, is an electrolyte abnormality disrupting the cellular membrane potential and transmission of action potentials [1].

- Risk of HK is mainly caused by factors related to the impaired function of circulation and metabolism, including chronic kidney disease (CKD), heart failure, diabetes mellitus, hypertension and use of Renin–angiotensin–aldosterone system inhibitors (RAASi) [2-6].

- The exacerbated clinical and economic burden associated with HK was commonly reported in recent studies based on different disease conditions and populations [7-10], with results varing in a comparatively large range.

- A better understanding of the short and long-term effects of HK across various regions is thus necessary due to the differences in the prevalence of risk factors, available treatment strategies and overall healthcare levels, but it has not been fully described in China.

- Therefore, this study addressed two objectives: (1) to investigate the association between the HK and all-cause mortality; (2) to assess the influence of HK on economic burdens with consideration of the observed survival conditions, including all-cause healthcare resource utilization (HRU) and direct medical costs.

METHODS

Data source

- Data of this retrospective cohort study were obtained from the Urban Employee Basic Medical Insurance (UEBMI) claims of Tianjin (2011-2017), which covers all of the urban employees and retirees of Tianjin.

Study population

- Adult patients (age ≥ 18 years) with newly-diagnosed CKD were first identified based on having ≥1 inpatient or outpatient visit with the diagnosis of CKD (ICD-10 codes E1x.2[x=0-4], I12, I13, N03, N04, N05, N18, N19, Z49, Z99.2, or free-text diagnosis) between Jan 1, 2012 to Dec 31, 2016.
- Patients who experienced ≥1 inpatient or outpatient visit with a diagnosis of HK (ICD-10 code E87.5 or free-text diagnosis) after being diagnosed with CKD were included in the HK cohort.
- A balanced non-HK cohort was formed by 1:1 propensity score matching based on baseline demographic and clinical characteristics.
- The index dates were defined as dates of the earliest identified HK event for patients in the HK cohort and then assigned to their counterparts in non-HK cohort.
- The included patients were required to be continuously enrolled during the 12 months prior (baseline period) to index date and 12 months follow-up from the index date, or death, whichever came first.

Study period

- The follow-up period was accumulated from the index date to the discontinued enrollment, death, or Dec 31, 2017, whichever came first.

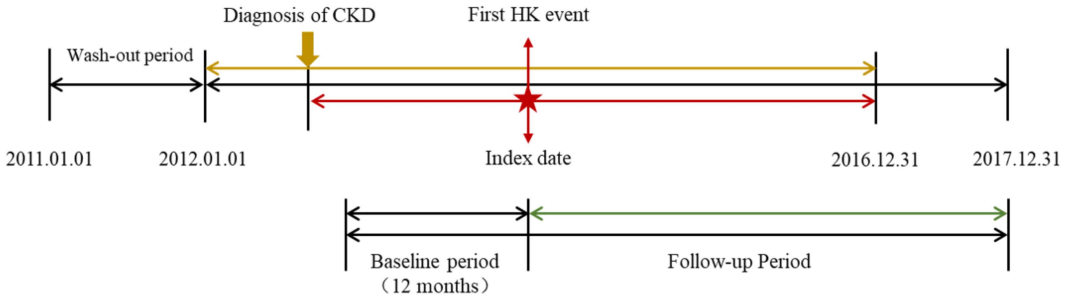


Figure 1. Overview of the study period

Study Measures

- Baseline comorbidities and medications of interest were risk factors of HK, including heart failure, diabetes mellitus, hypertension, and prescriptions of RAASi, etc. The baseline HRU was presented by number of annual outpatient and inpatient visits, as well as the annual total length of stay.
- Incidence of all-cause mortality was determined during the 12 months following the index events and the period from index date to the end of study, respectively.
- The all-cause HRU was assessed by the percentages of patients with inpatient and outpatient services, the numbers of hospitalizations and outpatient visits, as well as the annualized length of stay (ALOS) during the 12-month follow-up period.
- All-cause direct costs were estimated during the 12-month follow-up period and further attributed to costs of medications, examinations, nonmedication treatments (e.g., nursing and monitoring, etc.), surgery, medical consumables, and other medical services utilized (e.g., blood transfusion, etc.).

Data analysis

- The comparisons between HK and non-HK cohort were performed by Student's t-test, or $\chi 2$-test where appropriate.
- The Kaplan-Meier method and log-rank test were used to describe and compare the overall survival for HK and non-HK cohort.
- Hazard ratios (HRs) were calculated by Cox proportional hazard models to ascertain the association between HK and all-cause mortality.
- Kaplan-Meier sample average (KMSA) method was used to evaluate the differences in the HRU and costs between HK and non-HK cohorts accounting for the discrepancy of 12-month survival related with HK.
- The bootstrap approach was used to estimate the 95% confidence intervals (CIs) of KMSA estimators in which 1,000 iterations with 500 pairs of matched HK patients and controls were sampled.
- No further adjustment was presented in the analysis of mortality, HRU and costs, since the patient characteristics of HK and non-HK cohorts were balanced through matching.

RESULTS

Baseline characteristics (Table 1)

- 207,232 patients with new-onset CKD were identified between 2012 and 2016, among which 1,003 pairs of HK patients and matched controls (mean age 67.2±14.3 years, 40.3% female) were finally included in this study.
- The mean Charlson Comorbidity Index (CCI) score was 3.9 for both controls, with hypertension presented as the most common comorbidity, followed by dyslipidemia, type 2 diabetes mellitus, cardiovascular and cerebrovascular diseases.
- Concomitant medications were correspondingly frequent in both cohorts with around half of patients had prescriptions including calcium channel blockers, loop diuretics, NSAID and anti-platelet drugs, as well as angiotensin receptor blockers (ARB).
- Resource utilization and costs were high and similar during baseline period in the HK and non-HK cohort.

Table 1. Baseline characteristics of the HK and non-HK cohorts after propensity score matching

Variables	HK cohort N=1,003		non-HK cohort N=1,003		p-value	Standardized difference
	Mean/n	SD/%	Mean	SD/%		
Demographic characteristics						
Age at index date [Mean (SD)]	67.4	14.4	66.9	14.2	0.409	0.04
Female [n(%)]	407	40.6%	404	40.3%	0.891	0.01
CCI	3.9	2.6	3.9	2.3	0.943	0.00
CKD duration [month, mean(SD)]	12.7	15.3	12.8	13.5	0.767	-0.01
Baseline comorbidity [n(%)]						
Hypertension	796	79.4%	821	81.9%	0.158	-0.06
Dyslipidemia	465	46.4%	499	49.8%	0.129	-0.07
T2DM	440	43.9%	428	42.7%	0.589	0.02
Heart failure	204	20.3%	188	18.7%	0.368	0.04
CVD						
Arrhythmias	280	27.9%	285	28.4%	0.804	-0.01
Angina	208	20.7%	193	19.2%	0.402	0.04
Myocardial Infarction	98	9.8%	105	10.5%	0.604	-0.02
Other CVD	389	38.8%	411	41.0%	0.316	-0.04
CBD						
Stroke	309	30.8%	331	33.0%	0.292	-0.05
Transient Ischemic Attack	35	3.5%	39	3.9%	0.636	-0.02
Other CBD	121	12.1%	125	12.5%	0.785	-0.01
PVD	155	15.5%	168	16.7%	0.430	-0.04
Peptic ulcer	102	10.2%	93	9.3%	0.498	0.03
COPD	60	6.0%	68	6.8%	0.465	-0.03
Rheumatic disease	47	4.7%	52	5.2%	0.606	-0.02
Baseline treatment [n (%)]						
Dialysis	21	2.1%	13	1.3%	0.008	0.06
RAASi prescription						
ARB	482	48.1%	494	49.3%	0.592	-0.02
MRA	309	30.8%	324	32.3%	0.471	-0.03
ACEi	232	23.1%	235	23.4%	0.874	-0.01
Non-RAASi prescription						
Calcium channel blockers	639	63.7%	664	66.2%	0.242	-0.05
Loop Diuretics	540	53.8%	562	56.0%	0.324	-0.04
NSAID	537	53.5%	539	53.7%	0.929	0.00
Anti-platelet	475	47.4%	493	49.2%	0.421	-0.04
β-blocker	425	42.4%	450	44.9%	0.260	-0.05
Anti-dyslipidemia	392	39.1%	407	40.6%	0.494	-0.03
Insulin	374	37.3%	382	38.1%	0.712	-0.02
OAD	288	28.7%	279	27.8%	0.655	0.02
Bronchodilators	274	27.3%	276	27.5%	0.920	0.00
Anti-hypertension	231	23.0%	227	22.6%	0.832	0.01
All-cause healthcare resource utilization and total costs during the 12-month baseline period						
Number of hospitalizations per patient	1.3	1.7	1.3	2.2	0.865	-0.01
Total length of stay per patient	18.1	30.7	16.8	30.7	0.355	0.04
Number of outpatient visits per patient	35.9	35.3	35.8	32.2	0.939	0.00
All-cause total cost per patient	33,015	43,676	31,353	45,046	0.402	0.04

Abbreviations: SD, standard deviation; CCI, charlson comorbidity index; CKD, chronic kidney disease; HF, heart failure; T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease; CBD, cerebrovascular disease; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; MRA, mineralocorticoid receptor antagonists; OAD, oral antidiabetic drugs; NSAID, non-steroidal anti-inflammatory drugs.

Asssociation between HK and mortality

- The significant difference (log-rank test, P<0.001) of survival status between patients in HK and non-HK cohorts was observed during the 12-month follow-up period (Figure 2 (A)) and after a year from the index date (Figure 2 (B)).

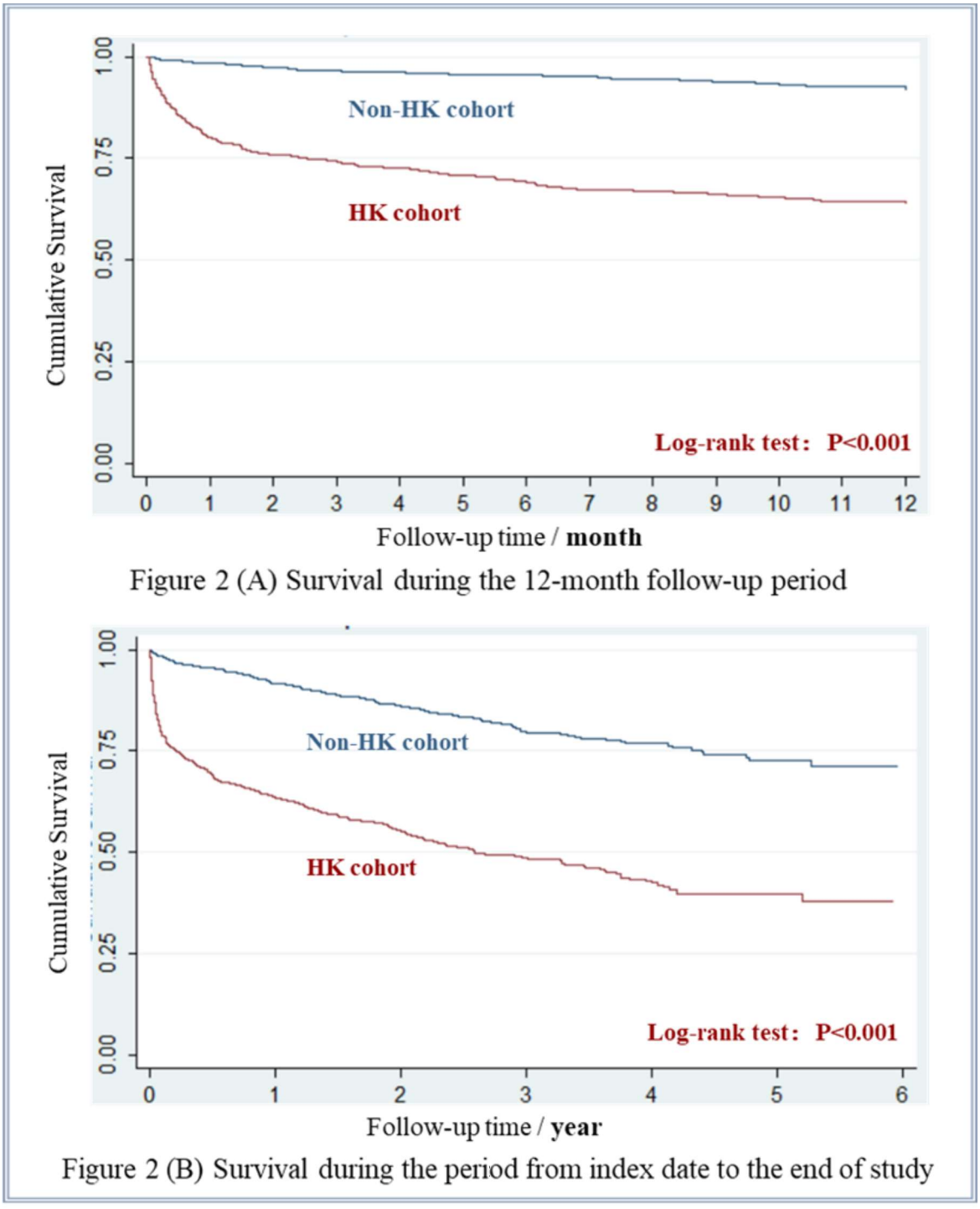


Figure 2. The Kaplan-Meier survival curves of HK and non-HK cohort

- 36.4% and 8.3% of patients in HK and non-HK cohorts died within the 12 months after index date, respectively, and a pronounced increased risk observed with a HR of 5.4 (95% CI: 4.2-6.8; Table 2).

- The ongoing increased risk of mortality was observed even after a year from the index date, with total rate of all-cause mortality during the period from index date to the end of study cumulated to be 49.5% in the HK cohort and 18.1% in the non-HK cohort, and a 3.7 (95% CI: 3.2-4.4) times of risk of all-cause mortality was observed (Table 2).

Table 2. Mortality of the HK and non-HK cohorts during the follow-up period

	HK cohort N=1,003	Non-HK cohort N=1,003	HR	95% CI	P-value
Mortality in the 12-month follow-up period	36.4%	8.3%	5.4	[4.2, 6.8]	<0.001
Mortality in the total follow-up period	49.5%	18.1%	3.7	[3.2, 4.4]	<0.001

The influence of HK on all-cause HRU

- More patients in the HK cohort (86.5% vs. 32.1%, P<0.001) experienced at least 1 hospitalization during the 12-month of follow-up period (Table 3).
- Patients in the HK cohort had on average one more hospitalization and stayed 20 more days in hospital compared to the non-HK cohort during the 12 months follow-up period (P<0.001, Table 3).
- The length of stay (15.8 vs. 12.7, P<0.01) and the mean cost (RMB 24,041 vs. RMB16,637, P<0.01) per admission was higher in the HK cohort among the 288 pairs of matched patients with at least 1 hospitalization compared to the non-HK cohort (Table 3), which is probably attributed to specialized medications, monitoring,examination and other interventions for the management or prevention of HK.
- For the total cohorts, less patients in the HK cohort (88.0% vs. 96.2, P<0.001) experienced at least 1 outpatient visit, probably due to the higher rate of hospitalization in this cohort. There were no difference in number of outpatient visits per patient in HK and the non-HK cohort.
- Among 849 matched patients with outpatient visits, the mean costs per visit were esimated to be ¥753 and ¥350 for HK and non-HK cohort, respectively (P<0.001, Table 3).

Table 3. The all-cause healthcare resource utilization and associated costs during the 12-month follow-up period

	HK cohort	Non-HK cohort	P-value
Inpatient services of total patients (N=1,003 for both cohorts) *			
Patients with at least 1 hospitalization	86.5%	32.1%	<0.001
Number of admissions per patient [mean(95%CI)]	1.9 (1.8-2.1)	0.7 (0.5-0.9)	<0.001
Total length of stay per patient [day, mean(95%CI)]	28.6 (25.0-31.7)	8.7 (6.5-10.5)	<0.001
Inpatient services of matched patients with hospitalizations (N=288 for both cohorts)			
Number of admissions [mean ± SD (median)]	2.1±1.5 (1.5)	2.1±3.1 (1.0)	0.946
Length of stay per admission [day, mean ± SD (median)]	15.8±13.5 (13.0)	12.7±11.8 (11.0)	<0.001
Direct medical cost per admission [¥, mean ±SD (median)]	24,041±28,975 (14,845)	16,637±22,429 (11,205)	<0.001
Outpatient services of total patients (N=1,003 for both cohorts)			
Patient with at least 1 outpatient visit	88.0%	96.2%	<0.001
Number of visits per patient [mean(95%CI)]	36.8 (33.0-40.8)	36.4 (33.4-39.4)	<0.001
Outpatient services of matched patients with outpatient visits (N=849 for both cohorts)			
Number of visit per patient [mean ± SD (median)]	41.0±48.2 (24)	37.7±34.9 (28)	0.109
Direct medical cost per visit [¥, mean ±SD (median)]	753±812 (479)	350±566 (227)	<0.001

Notes: Mean (95% CI) for variables estimated by KMSA method, mean ± standard deviation (median) for other variables
* The index hospitalizations were included.

RESULTS

The influence of HK on direct costs

- The incremental cost per patient during the 12 months follow up was significantly higher (¥38,479) in patients with HK vs non-HK cohort. This was primarily driven by higher inpatient costs (¥30,875) but outpatient costs were also higher in the HK cohort compared to the non-HK cohort (¥7,604, Table 4).

Table 4. The total all-cause direct medical costs in the 12-month follow-up period

	HK cohort N=1,003	Non-HK cohort N=1,003	Difference	P-value
Total all-cause direct medical costs[¥, mean(95%CI)]	59,120 (53,562-65,474)	20,732 (17,887-24,101)	38,479	<0.001
Inpatient costs [¥, mean(95%CI)]	41,855 (36,875-47,526)	10,980 (8,433-14,041)	30,875	<0.001
Outpatient costs [¥, mean(95%CI)]	17,355 (15,084-19,742)	9,752 (8,766-10,799)	7,604	<0.001

- The difference of total costs per patient during the first month after HK events (¥23,630 vs. ¥1,945, P<0.001, Figure 3(A)) was largely due to the sharp increase of inpatient costs during the first month after HK events (¥22,204 vs. ¥1,032, P<0.001, Figure 3(B)).

- The outpatient costs per patient in both cohorts were relatively stable with only slight growth observed among patients in the HK cohort during each time intervals (Figure 3(C)).

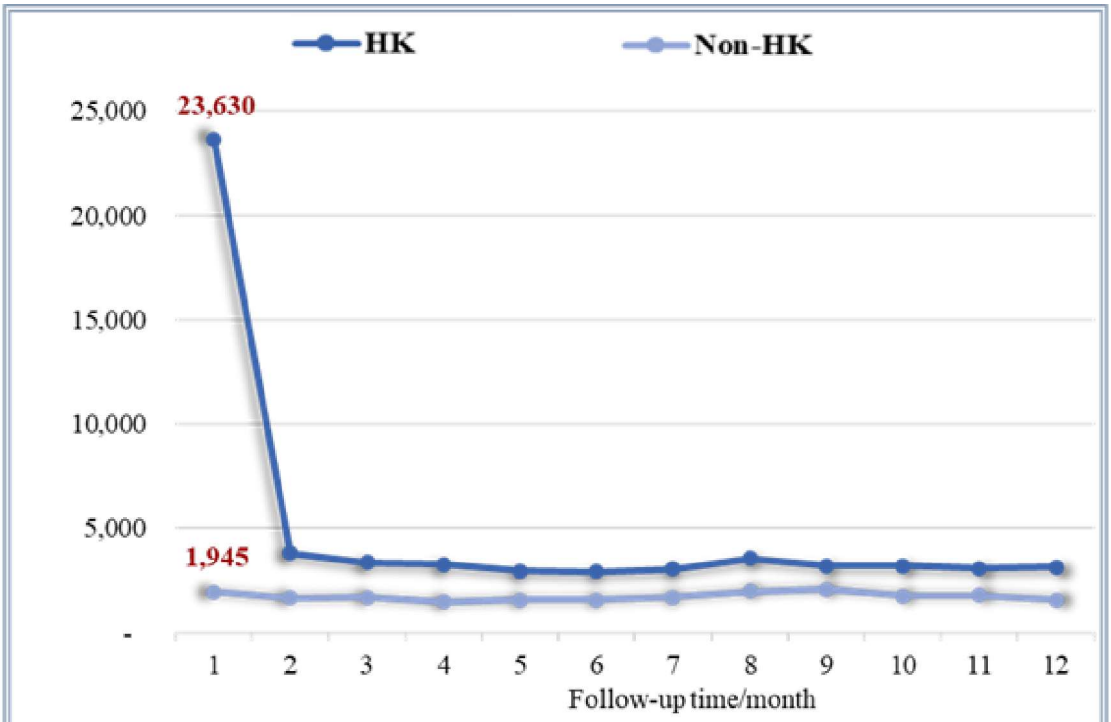


Figure 3 (A) Total costs per patient

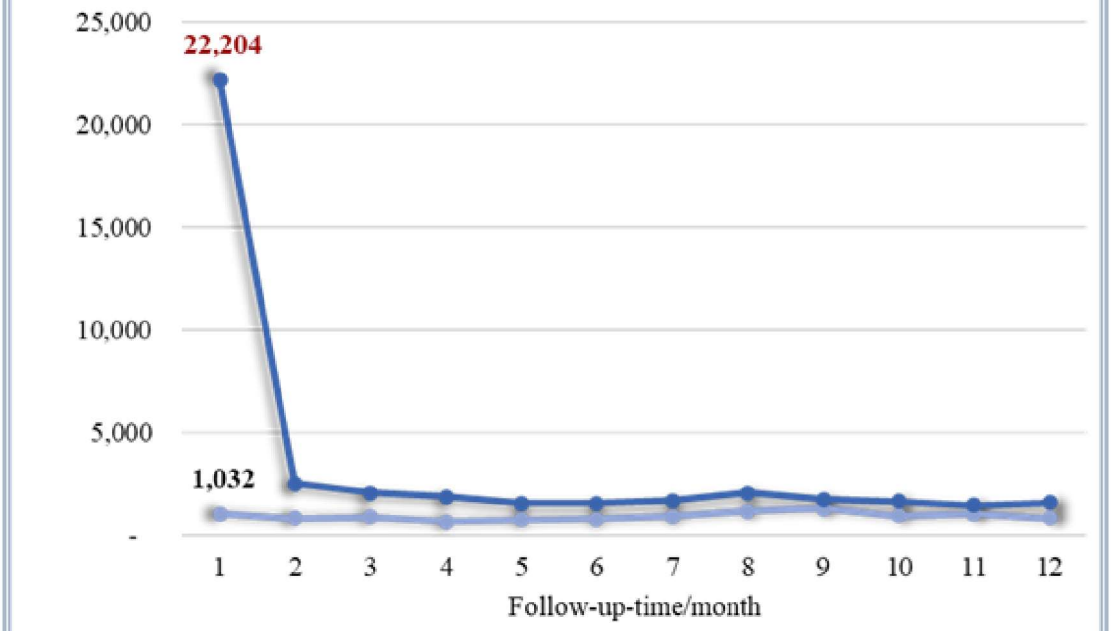


Figure 3 (B) Inpatient costs per patient

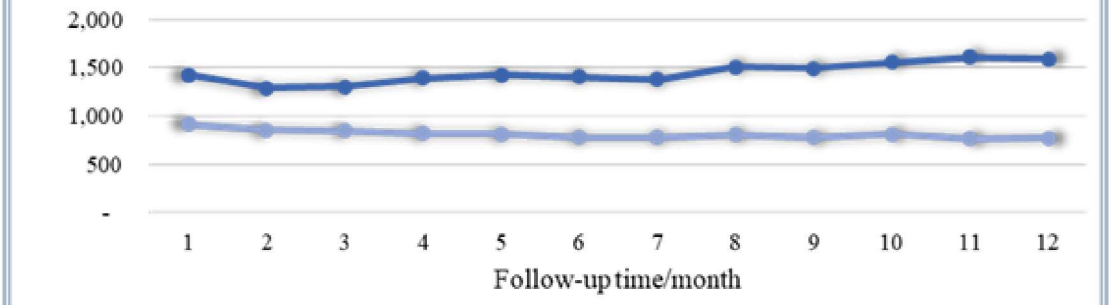


Figure 3 (C) Outpatient costs per patient

Figure 3. The monthly all-cause direct costs in the follow-up period

- The annual total direct costs in both cohorts were consistently driven by the costs of medication (45% in HK cohort and 60% in non-HK cohort), examinations (15% and 13% in HK and non-HK cohorts, respectively), and nonmedication treatments (23% and 11% in HK and non-HK cohorts, respectively, Figure 4).

- The higher percentage accounted by costs of nonmedication treatments in the HK cohort came from the outpatient costs (Figure 4(B)), which was possibly due to more visits in emergency department and higher hospital tiers. The patterns of inpatient costs were almost the same between the two cohorts.

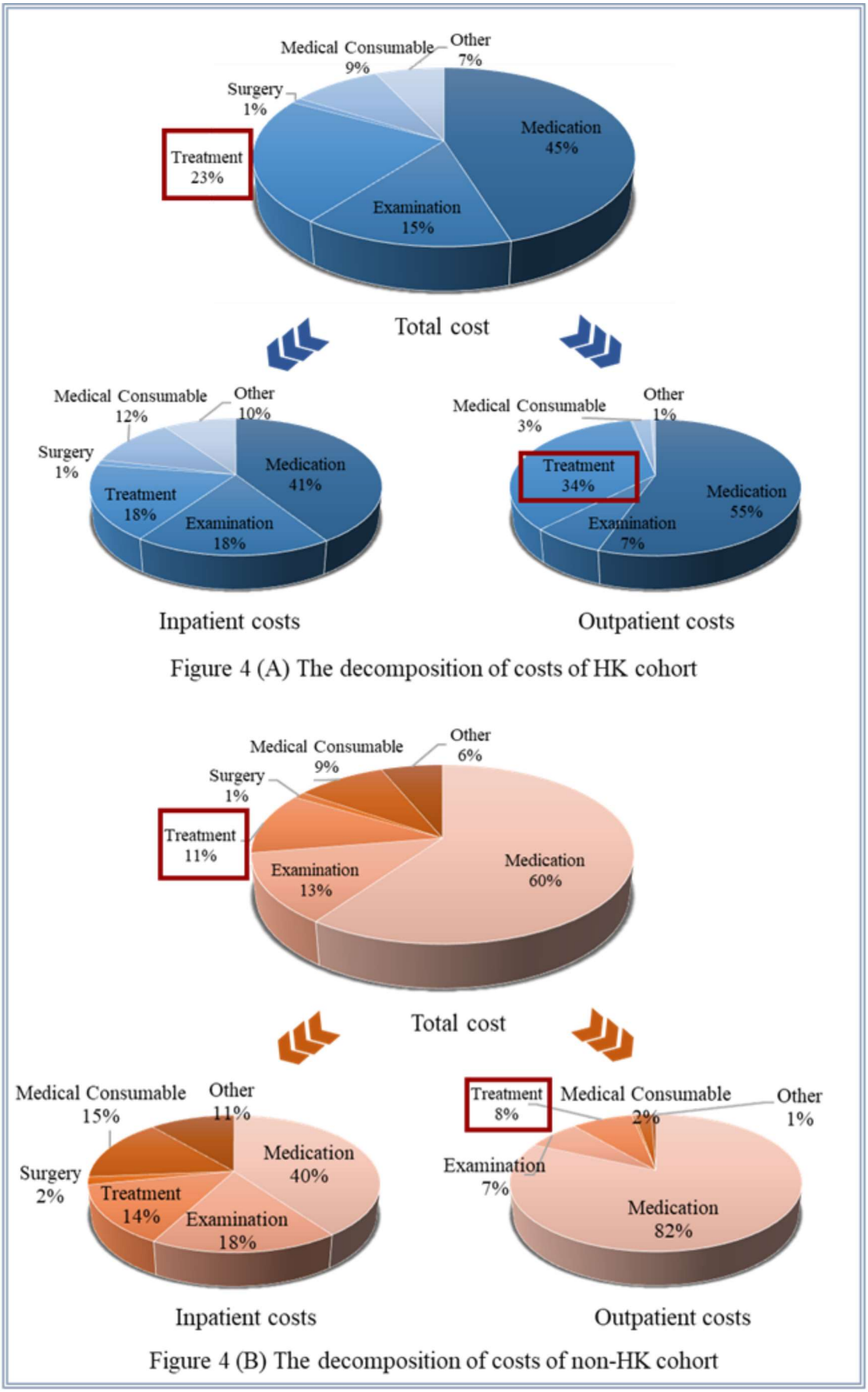


Figure 4. The decomposition of all-cause direct costs

Limitations

Limitations of this study were mainly associated with the use of retrospective claims data.

- Due to the unavailability of laboratory measures (e.g., eGFR and K+ level) in the used claims data, CKD, HK and other comorbidities were all identified through the diagnosis records in claims data, which may lead to the under-estimation of the prevalence of these diseases and also limited the detailed analysis of different subgroups according to disease severity.

- There are still some factors such as dietary habit, socioeconomic status that generally considered to be important confounders in retrospective study but unavailable in current claims database.

- The accociation between disease burden and the duration as well as recurrence of HK was not revealed in this study due to the lack of information on duration and relapsing events observed. It is possibly explained by the short duration of CKD in the included newly-diagnosed patients and under-identification of HK.

CONCLUSIONS

This is the first study estimating the impact of hyperkalemia on disease burden among patients with new-onset CKD in China. HK was a significant predicator of all-cause mortality for patients with CKD, especially during the immediate period after the hyperkalemic events. When compared with non-HK controls matched on baseline demographic and clinical characteristics, patients with HK incurred more utilization of healthcare services and greater all-cause total costs. The findings from this study indicate the need for effective management of HK in China to prevent adverse clinical outcomes and the associated healthcare resource utilization and cost burden.

References:

1. Mushiyakh Y, Dangaria H, Qavi S, et al. Treatment and pathogenesis of acute hyperkalemia[J]. Journal of Community Hospital Internal Medicine Perspectives, 2012, 1(4):7372-7372.

2. Kovesdy C P . Updates in hyperkalemia: Outcomes and therapeutic strategies[J]. Reviews in Endocrine and Metabolic Disorders, 2016, 18(1):41-47.

3. Linde C, et al. Serum potassium and clinical outcomes in heart failure patients: results ofrisk calculations in 21334 patients in the UK. ESC Heart Fail 2019 (6): 280–90.

4. Angela YM, et al. Optimally managing hyperkalemia in patients with cardiorenal syndrome. Nephrol Dial Transplant. 2019 Dec;1(34):36-44.

5. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. Am J Manag Care. 2015;21(11 Suppl):S212-20.

6. Lehnhardt A, Kemper MJ. Pathogenesis, diagnosis and management of hyperkalemia. Pediatr Nephrol. 2011;26: 377–384.

7. Luo J, Brunelli SM, Jensen DE, Yang A. Association between serum potassium and outcomes in patients with reduced kidney function. Clin J Am Soc Nephrol. 2016;11:90-100.

8. Horne L, Ashfaq A, Maclachlan S, et al. Epidemiology and health outcomes associated with hyperkalemia in a primary care setting in England[J]. BMC Nephrology, 2019, 20(1).

9. Jung, Nam, An, et al. Severe hyperkalemia requiring hospitalization: predictors of mortality. Critical care (London, England), 2012, 16(6):R225.

10. Kashihara N, Kohsaka S, Kanda E, et al. Hyperkalemia in Real-World Patients Under Continuous Medical Care in Japan[J]. Kidney International Reports, 2019, 4(9):1248-1260.