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Impacts of chronic kidney disease and other major non-communicable chronic diseases in China: a national study of 19.5 million hospitalizations

Running head: CKD and NCDs in China

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Abstract

Objective: To evaluate the impacts of chronic kidney disease (CKD) and other major non-communicable chronic diseases (NCDs) on healthcare system in China.

Design: Cross-sectional study.

Setting: A national in-patient database in tertiary hospitals in China.

Participants: 19.5 million hospitalizations of adult patients from July, 2013 to June, 2014. CKD and other major NCDs, including coronary heart disease (CHD), stroke, hypertension, diabetes, chronic obstructive pulmonary diseases (COPD), and cancer were extracted from the unified discharge summary form.

Outcome measures: Costs, length of hospital stay, and in-hospital mortality.

Results: The percentages with CKD, CHD, stroke, hypertension, diabetes, COPD, and cancer were 4.5%, 9.2%, 8.2%, 18.8%, 7.9%, 2.3%, and 19.4%, respectively. For each major NCD, the additional presence of CKD was independently associated with longer hospital stay, with increased percentages ranging from 7.69% (95% confidence interval [CI] 7.11%~8.28%, for stroke) to 21.60% (95% CI 21.09%~22.10%, for CHD). The hospital mortality of other NCDs was also higher in the presence of CKD, with fully adjusted relative risk from 1.91 (95% CI 1.82~1.99, for stroke) to 2.65 (95% CI 2.55~2.75, for cancer). Compared with other NCDs, CKD was associated with the longest hospital stay (22.1% increase), and resulted in the second highest in-hospital mortality, only lower than that of cancer (relative risk of 2.23 vs. 2.87).

Conclusions: The presence of diagnosed CKD alongside each major NCD was associated with an extra burden on healthcare system. The impacts of CKD on healthcare recourse utilization and prognosis were comparable to other major NCDs, which

highlights the importance of CKD as a major public health burden.

Keywords

Chronic kidney disease; Disease burden; Health care costs; Length of stay; Mortality; Non-communicable chronic disease

Strengths and limitations of this study

- The first national study that places the CKD burden on hospital stay and mortality in the full context of all major NCDs.
- With large sample size and wide geographical coverage.
- Only tertiary hospitals were included, which might lead to population selection bias.
- Diagnosis of major NCDs was based on the ICD-10 coding with low sensitivity.
- Data of eGFR or proteinuria and information on medications were not available.

Background

The spread of non-communicable diseases (NCDs) presents a global crisis, accounting for 68% of the world's deaths.[1] More importantly, more than 75% of NCDs-related deaths occurred in low- and middle-income countries, exerting a significant influence on healthcare costs.[2] Hence, the priority actions for the NCDs crisis, mainly heart disease, stroke, cancer, diabetes, and chronic respiratory diseases, were released in 2011.[1] The world leaders also committed to reduce premature deaths from NCDs by one-third by 2030.[2] Additionally, prevention and control of NCDs are important during this pandemic because NCDs and coronavirus disease 2019 (COVID-19) are closely connected.[3 4] They share a common set of underlying risk factors and patients with NCDs are more vulnerable to severe COVID-19 and death.[4]

In the past decade, chronic kidney disease (CKD) has been recognized as a major public health issue worldwide, with the estimated prevalence of more than 10%.[5 6] The burden of kidney diseases goes beyond its impact on the demand of kidney replacement therapy. CKD is a key determinant of the poor health outcomes of major NCDs and a risk multiplier in patients with cardiovascular disease (CVD), diabetes, and hypertension.[7] Due to the fact that the kidney is usually a target organ of systemic vascular, hemodynamic, metabolic, and inflammatory disorders, the pandemic of NCDs also leads to a persistently increasing morbidity of CKD.[8] Accumulating evidence based on individual disease revealed that major NCDs including heart disease and stroke had a worse prognosis in the presence of CKD.[9-11] Despite the underlying mechanisms not being fully understood, they might include: 1) CKD as a cause for adverse outcomes, 2) CKD as a marker of systematic disorders, and 3) therapeutic nihilism due to the presence

of CKD.[6]

While being realized as a global health issue, to the best of our knowledge, there is neither a large-scale study quantitatively evaluating the burden of CKD on all major NCDs, nor a study comparing the burden of CKD with other NCDs. In China, the world's most populous country, CKD is prevalent and associated with more severe comorbidities and higher medical expenditures.[12 13] However, evidence for the impacts of CKD and other major NCDs on the health care system at a national level is limited, which impedes the development of effective preventive strategies. Hence, we initiated this observational study, to comprehensively and quantitatively evaluate the impact of CKD on resource utilization and prognosis of other NCDs, as well as to compare the burden of kidney diseases on healthcare system with other NCDs among hospitalized patients in China.

Methods

Study population

The Hospital Quality Monitoring System (HQMS) is a mandatory patient-level national database for hospital accreditation under the authority of the National Health Commission of the People's Republic of China. Details of HQMS were described elsewhere.[14 15] In brief, all tertiary hospitals in China have been requested to submit electronic in-patient discharge records to HQMS on a daily basis. Different from those in the Western medical system, tertiary hospitals in China also provide primary, secondary, and tertiary care and have exposure to nationwide patient population. Patient-level data were collected from uniform front pages of hospitalization medical records. Altogether 353 variables including demographic characteristics, clinical diagnoses, procedures,

pathology diagnoses, and expenditure breakdowns were collected. All personal information has already been de-identified to protect patient privacy. The diagnoses were coded based on the International Classification of Diseases-10 (ICD-10) coding system by certified professional medical coders at every hospital. As the part of stringent standard practice in China, the front page has the legal validity and must be filed by the care given doctors who have the most accurate and comprehensive understanding of the patient's medical condition.

A total of 19,518,990 records of adult in-patients admitted from 1 July 2013 to 30 June 2014 in 29 provinces (excluding Hong Kong, Macao, Taiwan, Tibet, and Ningxia) were included in this cross-sectional study, with certain patients having more than one hospitalization. During this period, 715 tertiary hospitals in China, accounting for 44% of all tertiary hospitals in the country, had submitted in-patient records to HQMS database. Hospitalizations were used in the present analyses since it's more relevant to the discussion of "disease burden". This study was approved by the ethics committee of Peking University First Hospital (2015-928) and informed consent was waived by the ethics committee.

Definition of CKD

The ICD-10 coding of discharged diagnoses was used to identify patients with CKD.[14 15] Hospitalizations with at least one of the following diagnoses (in both primary diagnosis and secondary diagnoses) were identified as having CKD (relevant ICD-10 coding in supplemental appendix 1): glomerulonephritis, diabetic nephropathy, hypertensive nephropathy, obstructive nephropathy, renal cancer, tubulointerstitial nephritis, kidney

disease secondary to autoimmune diseases, kidney failure of unknown reason. Among patient-records with CKD, only 14% of them had the diagnoses of CKD staging.

Definition of other NCDs

Major NCDs, including coronary heart disease (CHD), stroke, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), and cancer,[1] were identified by the ICD-10 coding of hospital discharge diagnoses (in both primary and secondary diagnoses, relevant ICD-10 coding in supplemental appendix 1). Information on coronary angiography (CAG), percutaneous coronary intervention (PCI), and coronary artery bypass graft was obtained from the procedure coding of the front page for patients with CHD. For patients with multiple NCD diagnoses, each relevant diagnosis was identified and counted when stratified by the above NCDs.

Other covariates

Individual variables including age, sex, occupation (professional, worker, farmer, retirement, unemployment, and others), type of health insurance (basic medical insurance, new rural co-operative medical care, other types of insurance, and uninsured), type of admission (emergency, routine, and others), and intensive care unit (ICU) stay were collected from the front page.

Outcomes

Hospitalizations costs and length of hospital stay, which are both important indicators for healthcare resource utilization, were acquired from the front page. Information on in-

hospital mortality was also collected to assess the prognosis of patients. The survival status of each patient was verified based on the discharge status and combined with the information of autopsy.

Statistical analysis

General characteristics stratified by the presence of CKD for each NCD were described. Continuous data were presented as mean ± standard, or as median (inter-quartile range) for highly skewed variables. Categorical variables were presented as proportions. All analyses were based on the hospitalizations (patient-records), not individuals.

The effects of CKD on healthcare resource utilization for each NCD were analyzed using generalized linear regression models for log-transformed cost and length-of-stay. Poisson regression model was used to evaluate the impacts of CKD and other NCDs on in-hospital mortality. Percent of change and relative risk (RR) with 95% confidence interval (CI) were reported and calculated as exp(β)-1 and exp(β), respectively. For the purpose of accessing additional effects of CKD, covariates included in the model for the sub-dataset of each NCD were age (5-year categories, except for 18-25 years and >80 years), sex (male vs. female), type of health insurance (dummy variable), type of admission (dummy variable), ICU stay (yes vs. no), presence of CKD (yes vs. no), presence of other NCDs (yes vs. no), pneumonia (yes vs. no), and sepsis (yes vs. no).

Then the presence of CKD and other NCDs were included in the models simultaneously, using the data of all hospitalized patients, in order to compare the effect of CKD with other NCDs on outcome variables. Similar covariates were used as described previously.

For hospitalized patients with CHD, percentages of CAG and PCI were reported among different clinical types (including ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, and non-acute coronary syndrome), stratified by the presence of CKD. Among 18,315 hospitalizations with CHD and with diagnoses of CKD staging, percentages of CAG and PCI were also reported.

All analyses were performed using the SAS software, version 9.4 (SAS Institute Inc, Cary, NC). Due to the large sample size of our study, *P* values were not reported for between-group comparison.

Patient and public involvement statement

Patients or the public were not involved in this study.

Results

Among 19.5 million hospitalizations, the percentages of diagnosed CKD, CHD, stroke, hypertension, diabetes, COPD, and cancer were 4.5%, 9.2%, 8.2%, 18.8%, 7.9%, 2.3%, and 19.4%, respectively (table 1). For each major NCD, patient-records with CKD were older (except for hypertension), had a higher percentage of male, urban residents, ICU stay, and infectious diseases such as pneumonia and sepsis (except for COPD).

For each major NCD, the presence of CKD was independently associated with longer hospital stay, with increased percentages ranging from 7.69% (95% CI 7.11%~8.28%, for stroke) to 21.60% (95% CI 21.09%~22.10%, for CHD) (table 2). After adjusting for potential confounders, the presence of CKD was associated with higher costs for stroke (11.15%, 95% CI 10.31%~11.99%), COPD (19.46%, 95% CI

17.97%~20.97%), and cancer (18.88%, 95% CI 17.98%~19.78%), whereas the costs were slightly lower for CHD (acute coronary syndrome or non-acute coronary syndrome) (-1.08%, 95% CI -1.71%~-0.45%), hypertension (-0.22%, 95% CI -0.60%~0.16%), and diabetes (-0.97%, 95% CI -1.43%~-0.51%) in the presence of CKD (table 2). If patients with CHD were excluded, the presence of CKD was associated with increased costs for patients with hypertension and diabetes, with a fully adjusted change of 2.70% (95% CI 2.24%~3.15%) and 4.11% (95% CI 3.56%~4.66%), respectively. The in-hospital mortality was also higher in the presence of CKD for major NCDs, with fully adjusted RR from 1.91 (95% CI 1.82~1.99, for stroke; 95% CI 1.85~1.97, for hypertension) to 2.65 (95% CI 2.55~2.75, for cancer) (table 2).

Among hospitalizations with CHD, the percentages of CAG and PCI were substantially lower for those with CKD (figure 1). A similar pattern was observed for coronary artery bypass graft, which was 0.3% vs. 1.0% for CHD patients with or without CKD. Even for those with acute coronary syndrome or cardiogenic shock, a strong indication for emergency PCI,[16] the trend was still similar: 11.9% vs. 22.2% for ST-elevated myocardial infarction, and 3.5% vs. 7.3% for non-ST elevated myocardial infarction. Furthermore, among hospitalizations with diagnoses of CKD staging and with CHD, the percentages of CAG and PCI were lower even for stage 1-2, compared with those without CKD and with CHD (figure 1).

Compared with other NCDs, CKD had the most increase in length of hospital stay (22.09%, 95% CI 21.87%~22.32%) (table 3). Cancer and CHD were associated with the highest contribution to increased costs for hospitalized patients, which was 39.47% (95% CI 39.29%~39.65%) and 30.95% (95% CI 30.71%~31.19%), respectively. CKD was

associated with 6.82% (95% CI 6.56%~7.08%) increased costs. Furthermore, CKD resulted in the second highest in-hospital mortality (RR of 2.23, 95% CI 2.19~2.28), which was only lower than that of cancer (RR of 2.87, 95% CI 2.83~2.91).

Discussion

This study is the first national quantitative study on the burden of CKD and other major NCDs and their impacts on healthcare system in China. The findings of this study indicated that the presence of CKD was associated with extra burden on healthcare system and increased in-hospital mortality for each major NCD, despite evidence of under-utilization of cardiac procedures in the presence of CKD. Furthermore, the impacts of CKD on healthcare recourse utilization and mortality were comparable to other major NCDs in this large national sample of 19.5 million hospitalizations.

Studies regarding the utilization of healthcare resources for CKD mostly focused on end-stage kidney disease (ESKD).[17-19] The US Renal Data System 2019 Annual Data Report showed that costs on both CKD and ESKD were in excess of $120 billion in 2017, and the latter accounted for more than 7.2% of the total Medicare expenditure.[20] Our study revealed that CKD was associated with a 6.8% increase in costs, which was higher than that of hypertension, diabetes, and COPD. Moreover, for each major NCD, the presence of CKD led to longer hospital stay, which is also an important marker for healthcare resource utilization. Furthermore, considering evidence of therapeutic nihilism for patients with CKD (documented for cardiac revascularization) and the insensitivity of diagnostic codes for CKD, the impacts of CKD on healthcare system might be underestimated. A recent systematic review also showed that risks of adverse

cardiovascular outcomes increased with CKD and are associated with substantial additional costs and resource utilization.[21]

Several previous studies reported that both the general and high-risk population have worse prognoses in the presence of kidney diseases. For example, using the data of 1.1 million adults within a large integrated healthcare system, Go AS *et al* observed increased risks of all-cause mortality, CVD, and hospitalization associated with reduced kidney function.[9] A recent meta-analysis reported that both reduced estimated glomerular filtration rate (eGFR) and elevated urinary albumin-to-creatinine ratio were associated with increased all-cause and cardiovascular mortality in the general population.[22] Similarly, using data from over 40 cohorts involving one million participants, it was reported that the adjusted hazard ratio for all-cause mortality at eGFR 45 ml/min/1.73m^2 was 1.24 (95% CI 1.11~1.39) for those with hypertension,[23] and was 1.35 (95% CI 1.18~1.55) for those with diabetes,[24] compared with those with eGFR of 95 ml/min/1.73m^2. In this study, we further expanded the observation to a range of other major NCDs, including CHD, stroke, COPD, and cancer. We found that CKD was consistently associated with increased in-hospital mortality for each major NCD and its impact was higher compared with the majority of NCDs, even comparable to that of cancer. These findings further highlight the importance of CKD as a major health burden and are consistent with the implications of Global Burden of Disease, Injuries, and Risk Factors Study, which has showed the high burden and rapid growth of CKD as a direct cause of morbidity and mortality.[5 25]

The potential mechanisms for the association of CKD with adverse outcomes are not fully understood, although there are several possible explanations. First, a previous study

indicated that impaired kidney function could lead to multiple adverse systemic alterations, including inappropriate activation of the renin-angiotensin system, catalytic iron-dependent oxidative stress, endothelial dysfunction, and inflammation.[11] Furthermore, an elevated blood phosphate level accompanied by impaired kidney function has been associated with increased cardiovascular risk,[26] perhaps through its direct effect on vascular calcification,[27] as well as through elevated levels of phosphaturic hormones such as fibroblast growth factor 23.[28] In addition, CKD is associated with alterations in primary host defense mechanisms, thus increasing the risk of infection.[29] Second, appropriate adjustment of drug dosage according to the kidney function is important for reducing medication errors and ensuring optimal patient outcomes.[30] In developing countries like China, this is aggravated by unmet needs for both hospital and community pharmacists.[31] Finally, for patients whose CKD is a result of systemic disease such as diabetes, kidney diseases might only serve as a marker of the severity of the target organ damage.

Another explanation for the adverse outcome observed in patients with CKD might be that the presence of CKD is associated with reduced implementation of best practice. Despite that accumulating evidence and the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines with international consensus suggest that the level of care for ischemic heart disease offered to patients with CKD should not be prejudiced by their CKD,[29] our data on revascularization indicates that cardiac treatment for patients with CKD is sub-optimal. Under-utilization of aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, glycoprotein IIb/IIIa receptor antagonists, and thrombolytic therapy has been observed in CKD patients due to concerns of bleeding risk, worsening of kidney

function, and comorbidities.[32] A recent study from the United States indicated that compared with those without CKD, patients with CKD reported more medication use for cardiovascular risk factor but had poorer risk factor control.[33] In our study, the percentages of CAG and PCI were much lower for hospitalizations with CKD, even for those with relatively well-preserved kidney function, consistent with practice outside of China.[32] A recent meta-analysis revealed that for patients with pre-dialysis CKD and with unstable angina or non-ST segment elevation myocardial infarction, an early invasive strategy was associated with the risk of re-hospitalization and trends of reduction in the risk for death and non-fatal re-infarction.[34] However, the risk of adverse clinical events after coronary revasculization and the percentage of later additional PCI were also increased for patients with CKD.[35 36] Hence, a multi-disciplinary team involving various sub-specialties is needed to improve the quality of care for CKD patients and appropriate management by primary care clinicians are necessary to prevent CKD-associated adverse outcomes.[37]

To our knowledge, this is the first study that places the CKD burden on hospital stay and mortality in the full context of all major NCDs in a national database with large sample size and wide geographical coverage, which enables us to compare the impacts of multiple major NCDs simultaneously. However, our study does have some limitations. First, although our data are restricted to hospitalized patients, hospitalization inherently reflects indication for admission and referral as well as disease burden. Only tertiary hospitals were included in our analyses, which might lead to population selection bias; but 715 hospitals in our study covered almost all provinces of China and included all types of tertiary hospitals. Second, the diagnosis of CKD and major NCDs in hospitalized

patients was based on the ICD-10 coding with low sensitivity. We have performed a validation study using data of 67,376 patients from 3 hospitals in HQMS database. The sensitivity and specificity of CKD identification by discharge diagnoses were 34.2% and 97.8%, respectively.[38] Severe cases of CKD were likely to be diagnosed, which might lead to a potential overestimation of the excess risk associated with CKD. However, the high specificity and accuracy of definition for patients with CKD are the strengths of our study. Finally, data of eGFR or proteinuria and information on medications used and the severity of major NCDs were not available for all patient-records in our dataset.

Conclusions

Our study revealed that in a systematic national assessment of diagnosed NCDs over 19.5 million hospitalizations in China, the adverse effects of CKD at both individual level and healthcare system level were comparable to other major NCDs and the presence of CKD was associated with poor prognosis of other NCDs. Therefore, CKD should be integrated into the global prevention strategy of NCDs. In consideration of the complexity of the disease, a multi-level interdisciplinary approach will be needed to address the public health burden of CKD.

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Contributors

HW and LZ conceived and coordinated the study and acquired the data. CY, HW, and LZ designed the study. CY and LZ searched the literature. CY and JL prepared the figure. CY, HW, and LZ wrote the first draft manuscript. CY, JL, SY, and ZZ contributed to the analysis. CY, JL, SY, ZZ, JW, M-HZ, HW, LZ, and JC contributed to the interpretation. CY, JL, SY, ZZ, JW, M-HZ, HW, LZ, and JC edited the manuscript. All authors critically reviewed the manuscript and approved the final version.

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Competing interests

LZ received research funding from AstraZeneca. JC was partly supported by grants to the CKD Prognosis Consortium by the National Kidney Foundation and NIH.

Patient and public involvement statement

Patients or the public were not involved in this study.

Patient consent for publication

Not required.

Ethics approval

Ethical approval was obtained from the ethics committee of Peking University First Hospital (2015-928).

Data availability statement

The data that support the findings of this study are available from the Bureau of Medical Administration and Medical Service Supervision, National Health Commission of China but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Bureau of Medical Administration and Medical Service Supervision, National Health Commission of China.

Supplementary material

Appendix 1. The International Classification of Diseases-10 coding of chronic kidney disease and other major non-communicable chronic diseases

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Figure 1. Percentages of coronary angiography and percutaneous coronary intervention for hospitalizations with coronary heart disease

Note: The number of hospitalizations with or without CKD was 3,116 and 68,616 for STEMI, 2,645 and 25,057 for NSTEMI, 124,388 and 1,519,864 for NACS, respectively. For 18,315 hospitalizations with diagnoses of CKD staging, 15.8%, 24.6%, 16.8%, and 42.9% of them were in stage 1-2, 3, 4 and 5.

Abbreviations: CKD, chronic kidney disease; NACS, non-acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

Table1. Characteristics of hospitalized patients with non-communicable chronic diseases stratified by the presence of chronic kidney disease

	CHD		Stroke		Hypertension		Diabetes		COPD		Caner		Total	
	CKD	Non-CKD	CKD	Non-CKD	CKD	Non-CKD	CKD	Non-CKD	CKD	Non-CKD	CKD	Non-CKD	CKD	Non-CKD
Number	132032	1665601	79 906	1529843	348075	3322665	222157	1321816	22998	429475	8025	3698423	871742	18647248
Percentage (%)	0.7	8.5	0.4	7.8	1.8	17.0	1.1	6.8	0.1	2.2	0	19.0	4.5	95.5
Age (years)	71.4±11.8	68.1±12.0	69.1±13.0	65.9±12.9	64.7±14.3	65.7±12.3	63.7±13.2	63.3±12.8	76.7±9.6	72.8±10.3	62.4	3.8	56.7±13.3	57.7±17.0	52.7±17.6
Male (%)	60.2	55.4	62.6	55.1	59.4	52.2	57.6	53.1	76.6	71.7	6		49.7	57.3	45.6
Occupation (%)†															
Professional	7.6	8.7	8.0	8.5	9.8	9.2	11.0	11.2	4.2	4.2	1		11.1	11.9	14.4
Worker	4.9	5.3	5.6	5.9	5.9	5.9	6.5	6.3	3.8	4.7	6		6.2	6.6	7.1
Farmer	11.8	18.1	15.7	23.0	15.6	19.1	14.7	15.8	15.2	23.2	1		24.7	21.3	21.5
Retirement	40.9	32.4	36.6	27.7	30.6	28.7	31.0	28.3	42.3	31.3	2		14.5	20.7	13.8
Unemployment	7.0	6.3	7.1	7.4	8.6	7.3	8.7	7.4	7.5	7.8	8		9.7	9.4	10.1
Others	27.8	29.4	27.0	27.4	29.5	29.9	28.2	31.1	27.1	28.9	3		33.7	30.2	33.1
Health insurance (%)															
Basic medical insurance	66.0	59.0	62.7	54.0	59.6	57.0	62.3	59.9	63.1	54.3	5		43.0	49.9	42.9
NRCMC	12.5	18.7	15.8	22.6	16.9	19.4	15.8	16.7	15.5	24.4	1		26.7	23.2	22.5
Others	11.0	11.6	9.8	10.3	10.6	10.3	9.9	10.3	10.2	10.0	1		12.7	11.4	13.0
Uninsured	10.5	10.8	11.8	13.1	12.9	13.3	12.0	13.1	11.2	11.3	1		17.6	15.4	21.6
Admission (%)†															
Emergency	21.6	22.6	25.3	29.3	17.3	20.5	16.5	16.9	22.9	23.1	1		7.4	16.1	17.9
Routine	71.6	69.4	68.3	63.2	76.0	72.2	76.6	75.1	69.1	68.9	8		82.4	76.0	72.6
Others	6.8	7.9	6.5	7.6	6.7	7.4	6.9	8.0	8.0	8.0	9		10.2	7.9	9.5
ICU stay (%)	4.1	3.0	3.9	2.7	2.4	2.0	2.2	1.7	5.1	3.2	2		0.7	2.0	1.2
Hypertension (%)	69.6	55.3	71.1	56.6	--	--	62.7	52.6	54.8	33.6	37		12.2	39.9	17.8
CHD (%)	--	--	28.2	18.7	26.4	27.7	26.8	25.8	35.9	23.0	9		2.9	15.2	8.9
Stroke (%)	17.1	17.1	--	--	16.3	26.0	14.8	18.9	12.7	9.5	4		1.8	9.2	8.2
COPD (%)	6.2	5.9	3.7	2.7	3.6	4.3	2.6	3.1	--	--	2		1.1	2.6	2.3
Cancer (%)	5.7	6.5	4.9	4.4	7.5	13.5	5.0	13.4	7.9	9.6			--	9.2	19.8
Diabetes (%)	45.0	20.5	41.2	16.3	40.0	20.9	--	--	24.6	9.6	1		4.8	25.5	7.1
Pneumonia (%)	6.1	4.1	5.8	3.6	4.3	3.6	4.3	3.4	8.3	8.5	3		2.0	3.7	2.3
Sepsis (%)	0.5	0.2	0.7	0.2	0.5	0.2	0.7	0.3	0.7	0.3	0		0.2	0.6	0.2
Costs (1000 yuan)	11(7-20)	9(6-20)	11(7-19)	9(6-16)	10(6-17)	9(6-16)	10(7-16)	9(6-16)	12(8-22)	10(6-16)	15(8-29)		10(6-20)	9(6-17)	8(4-14)
Length-of-stay (days) †	11(8-17)	9(6-13)	12(8-17)	11(7-15)	11(7-16)	9(6-14)	12(8-16)	10(7-14)	12(8-19)	10(7-15)	12(8-19)		8(4-14)	11(6-16)	8(5-13)
Mortality (%)	3.5	1.4	3.5	1.5	1.8	0.9	1.8	0.9	4.9	1.9	5		1.0	1.8	0.6

[†]The percentages of missing values for occupation, type of admission and length of stay was 10.9%, 6.4%, and 16.6% for CHD; 10.5%, 7.1%, and 17.5% for stroke; 10.7%, 6.7%, and 16.2% for hypertension; 10.7%, 6.9%, and 16.6% for diabetes; 12.2%, 5.4%, and 18.0% for COPD; 11.4%, 6.1%, and 15.2% for cancer.

Abbreviations: CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; NCDs, non-communicable chronic diseases; NRCMC, New Rural Co-operative Medical Care.

Table 2. Effects of chronic kidney disease on length of stay, costs, and in-hospital mortality for each non-communicable disease

Condition	Covariates in the model	Length of stay % change (95% CI)	Costs % change (95% CI)	In-hospital mortality relative risk (95% CI)
CHD	Model 1	24.58 (24.1, 25.06)	4.96 (4.34, 5.58)	2.15 (2.08, 2.22)
	Model 2	21.99 (21.49, 22.5)	-0.26 (-0.90, 0.37)	2.09 (2.02, 2.16)
	Model 3	21.60 (21.09, 22.10)	-1.08 (-1.71, -0.45)	2.02 (1.95, 2.09)
Stroke	Model 1	11.35 (10.80, 11.90)	16.65 (15.81, 17.49)	2.17 (2.08, 2.26)
	Model 2	8.26 (7.68, 8.85)	13.05 (12.19, 13.91)	2.01 (1.92, 2.10)
	Model 3	7.69 (7.11, 8.28)	11.15 (10.31, 11.99)	1.91 (1.82, 1.99)
Hypertension	Model 1	14.46 (14.17, 14.74)	-0.40 (-0.76, -0.04)	1.94 (1.89, 2.00)
	Model 2	16.24 (15.92, 16.55)	0.49 (0.10, 0.87)	1.97 (1.91, 2.03)
	Model 3	16.01 (15.70, 16.33)	-0.22 (-0.60, 0.16)	1.91 (1.85, 1.97)
Diabetes	Model 1	14.05 (13.70, 14.41)	-2.90 (-3.33, -2.47)	1.88 (1.82, 1.95)
	Model 2	16.55 (16.16, 16.94)	-0.14 (-0.60, 0.33)	2.02 (1.94, 2.10)
	Model 3	16.32 (15.93, 16.70)	-0.97 (-1.43, -0.51)	1.95 (1.88, 2.03)
COPD	Model 1	15.85 (14.84, 16.87)	31.41 (29.78, 33.06)	2.21 (2.08, 2.35)
	Model 2	11.14 (10.11, 12.18)	20.15 (18.65, 21.68)	1.99 (1.86, 2.13)
	Model 3	11.05 (10.02, 12.09)	19.46 (17.97, 20.97)	1.97 (1.84, 2.11)
Cancer	Model 1	21.38 (20.66, 22.11)	25.84 (24.96, 26.72)	3.30 (3.19, 3.41)
	Model 2	17.87 (17.11, 18.64)	19.63 (18.72, 20.54)	2.75 (2.65, 2.85)
	Model 3	17.50 (16.74, 18.26)	18.88 (17.98, 19.78)	2.65 (2.55, 2.75)

Note: Numbers in the table are percent-changes/relative risks of patient-record with CKD compared with patient-record without CKD for each non-communicable disease.

Covariates in model 1 included age and sex.

Covariates in model 2 included age, sex, occupation, type of health insurance, type of admission, intensive care unit stay, presence of CHD, stroke, hypertension, diabetes, COPD, and cancer (except for the disease used to define the subgroup).

Covariates in model 3 included covariates in model 2, plus the presence of sepsis and pneumonia.

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

Table 3. Effects of chronic kidney disease on length of stay, costs, and in-hospital mortality - comparisons with other major non-communicable diseases

Condition	Covariates in the model	Length of stay % change (95% CI)	Costs % change (95% CI)	In-hospital mortality relative risk (95% CI)
CKD	Model 1	22.34 (22.14, 22.55)	6.49 (6.25, 6.73)	2.31 (2.27, 2.35)
	Model 2	22.09 (21.87, 22.32)	6.82 (6.56, 7.08)	2.23 (2.19, 2.28)
CHD	Model 1	-5.19 (-5.31, -5.07)	27.72 (27.51, 27.94)	1.36 (1.34, 1.38)
	Model 2	-7.31 (-7.44, -7.18)	30.95 (30.71, 31.19)	1.31 (1.29, 1.33)
Stroke	Model 1	16.12 (15.97, 16.27)	9.29 (9.10, 9.48)	1.58 (1.56, 1.60)
	Model 2	17.34 (17.17, 17.51)	9.90 (9.69, 10.11)	1.70 (1.67, 1.73)
Hypertension	Model 1	5.49 (5.39, 5.59)	8.90 (8.77, 9.04)	0.93 (0.92, 0.94)
	Model 2	1.81 (1.69, 1.92)	4.85 (4.70, 5.01)	0.76 (0.75, 0.77)
Diabetes	Model 1	11.36 (11.22, 11.51)	5.05 (4.87, 5.23)	1.13 (1.11, 1.15)
	Model 2	8.96 (8.80, 9.12)	1.00 (0.81, 1.20)	0.99 (0.97, 1.01)
COPD	Model 1	3.89 (3.65, 4.14)	-9.00 (-9.29, -8.71)	1.31 (1.28, 1.34)
	Model 2	5.77 (5.50, 6.04)	-8.67 (-8.98, -8.36)	1.24 (1.21, 1.27)
Cancer	Model 1	8.90 (8.80, 9.00)	27.40 (27.25, 27.55)	2.00 (1.97, 2.02)
	Model 2	13.90 (13.79, 14.02)	39.47 (39.29, 39.65)	2.87 (2.83, 2.91)

Note: Numbers in the table are percent-changes/relative risks of patient-record with corresponding disease compared with patient-record without corresponding disease.

Covariates in model 1 included age and sex.

Covariates in model 2 included age, sex, occupation, type of health insurance, type of admission, intensive care unit stay, presence of CKD, CHD, stroke, hypertension, diabetes, COPD, and cancer, and presence of sepsis and pneumonia.

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

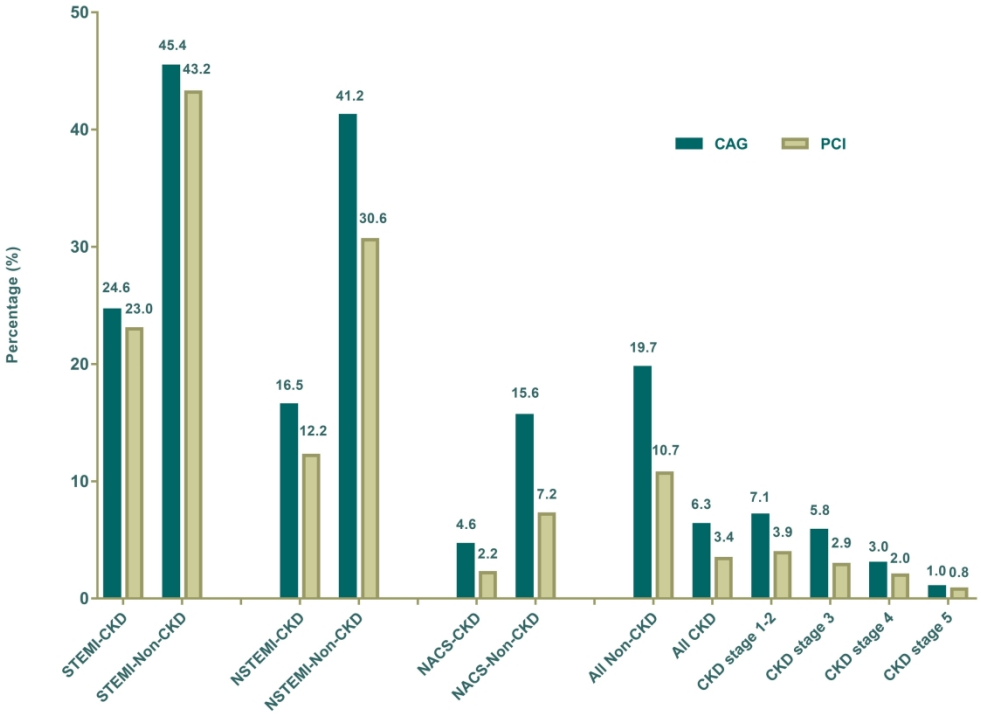

Figure 1. Percentages of coronary angiography and percutaneous coronary intervention for hospitalizations with coronary heart disease

Note: The number of hospitalizations with or without CKD was 3,116 and 68,616 for STEMI, 2,645 and 25,057 for NSTEMI, 124,388 and 1,519,864 for NACS, respectively. For 18,315 hospitalizations with diagnoses of CKD staging, 15.8%, 24.6%, 16.8%, and 42.9% of them were in stage 1-2, 3, 4 and 5.

Abbreviations: CKD, chronic kidney disease; NACS, non-acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

227x170mm (300 x 300 DPI)

Appendix 1. The International Classification of Diseases-10 coding of chronic kidney disease and other major non-communicable chronic diseases

Disease		ICD-10 coding
CKD		E10.2+, E11.2+, E13.2+, E14.2+, I12.0, I12.9, I13.0, I13.1, I13.2, I13.9, N11, N12, N14, N15, N16.*, E74.8, E72.0, N25.1, M32.1+N08.5*, M32.1+N16.4*, M35.0+N16.4*, M31.0+N08.5*, M31.7+N08.5*, M31.001‡, M31.802‡, M32.101+N08.5*†, M31.102+N08.5*†, M31.303+N08.5*†, N18, N19, N13.0, N13.1, N13.2, C64, N07, N08 (excluding N08.5*), N13.6, Q60, Q61.1, Q61.2, Q61.3, Q61.5, Q63.1, Q63.9, M10.3, N26, N28.0, N28.8, N28.9, A52.7+N08.0*, N99.0, P96.0, R39.2, K76.7, Q27.1, I70.1, M31.4 (combined with I15.0) E10.2+, E11.2+, E13.2+, E14.2+ N00.8, N02, N03, N04, N05, N06, N39.1
CHD	CHD†	I21.001, I21.002, I21.004, I21.101, I21.103, I21.104, I21.105, I21.201, I21.202, I21.203, I21.204, I21.205, I21.206, I21.207, I21.208, I21.209, I21.210, I21.211, I21.213, I21.214, I21.215, I21.301, I21.302, I21.304, I21.907, I21.403, I24.803, I20.001, I20.002, I20.003, I20.004, I20.005, I20.006, I20.101, I20.102, I20.802, I20.803, I21.303, I21.401, I21.402, I21.901, I21.902, I21.910, I22.001, I22.101, I22.801, I22.802, I22.803, I22.901, I23.001, I23.002, I23.101, I23.201, I23.301, I24.001, I24.002, I24.003, I24.004, I24.005, I24.006, I24.101, I24.102, I24.801, I24.802, I24.901, I20.801, I20.804, I20.805, I20.806, I20.902, I25.103, I25.104, I25.105, I25.201, I25.202, I25.203, I25.204, I25.205, I25.206, I25.207, I25.208, I25.209, I25.210, I25.211, I25.212, I25.213, I25.214, I25.215, I25.501, I25.601, I25.901, I25.902
	CHD‡	I21.000, I21.001, I21.002, I21.003, I21.004, I21.005, I21.006, I21.007, I21.100, I21.101, I21.102, I21.103, I21.104, I21.105, I21.200, I21.201, I21.202, I21.203, I21.204, I21.205, I21.206, I21.300, I21.301, I21.401, I20.000, I20.001, I20.002, I20.003, I20.004, I20.005, I20.006, I20.100, I20.101, I20.102, I20.804, I21.302, I21.303, I21.400, I21.402, I21.900, I22.000, I22.100, I22.800, I22.900, I23.000, I23.100, I23.200, I23.300, I23.400, I23.500, I23.600, I23.601, I23.800, I24.000, I24.001, I24.100, I24.101, I24.800, I24.801, I24.900, I24.901, I20.801, I20.802, I20.803, I20.804, I20.900, I25.000, I25.100, I25.101, I25.102, I25.103, I25.200, I25.500, I25.600, I25.800, I25.801, I25.900, I25.901,
COPD		J44.901†, J44.003†, J44.103†, J44.900‡, J44.000‡, J44.100‡, J44.800‡
Stroke		I60, I61, I63, I64, G45, H34.1
Cancer		C00-C26, C30-C34, C37-C41, C43-C58, C60-C85, C88, C90-C97, D00-D07, D09, D37-D48, B21, Z85, Z08 Z51.10†, Z51.20†, Z51.50†, Z03.101†, E87.805†, O99.8011†, O99.8021†, O99.8024†, O99.8031†, Z51.00‡, Z51.10‡, Z51.80‡, Z03.10‡, O99.802‡, Z35.802‡, Z54.001‡, E88.805‡, Z86.000‡
Hypertension		I10

Disease	ICD-10 coding
Sepsis	A41
Pneumonia	J12-J18

†Applicable for ICD-10 (Beijing Version 4.0) only.

‡Applicable for ICD-10 (National Standard Version1.0) only.

Abbreviations: CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary diseases. ICD-10, International Classification of Diseases-10.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-10
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	10
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	-
Outcome data	15*	Report numbers of outcome events or summary measures	11-13

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	11-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Impacts of chronic kidney disease and other major non-communicable chronic diseases on healthcare resource utilization in China: a cross-sectional study

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Impacts of chronic kidney disease and other major non-communicable chronic diseases on healthcare resource utilization in China: a cross-sectional study

Running head: CKD and NCDs in China

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Abstract

Objective: To evaluate the impacts of chronic kidney disease (CKD) and other major non-communicable chronic diseases (NCDs) on healthcare system in China.

Design: A cross-sectional study.

Setting: A national inpatient database in tertiary hospitals in China.

Participants: A total of 19.5 million hospitalizations of adult patients from July, 2013 to June, 2014. Information on CKD and other major NCDs, including coronary heart disease (CHD), stroke, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), and cancer was extracted from the unified discharge summary form.

Outcome measures: Costs, length of hospital stay, and in-hospital mortality.

Results: The percentages of hospitalizations with CKD, CHD, stroke, hypertension, diabetes, COPD, and cancer were 4.5%, 9.2%, 8.2%, 18.8%, 7.9%, 2.3%, and 19.4%, respectively. For each major NCD, the additional presence of CKD was independently associated with longer hospital stay, with increased percentages ranging from 7.69% (95% confidence interval [CI], 7.11%–8.28%) for stroke to 21.60% (95% CI, 21.09%–22.10%) for CHD. The hospital mortality for other NCDs was also higher in the presence of CKD, with fully adjusted relative risk ranging from 1.91 (95% CI, 1.82–1.99) for stroke to 2.65 (95% CI, 2.55–2.75) for cancer. Compared with other NCDs, CKD was associated with the longest hospital stay (22.1% increase) and resulted in the second highest in-hospital mortality, only lower than that of cancer (relative risk, 2.23 vs. 2.87, respectively).

Conclusions: The presence of diagnosed CKD alongside each major NCD was associated with an additional burden on the healthcare system. The impacts of CKD on

healthcare resource utilization and prognosis were comparable to those of other major NCDs, which highlights the importance of CKD as a major public health burden.

Keywords

Chronic kidney disease; Disease burden; Health care costs; Length of stay; Mortality; Non-communicable chronic disease

Strengths and limitations of this study

- The first national study placing the CKD burden on hospital stay and mortality in the full context of all major NCDs.
- Large sample size and wide geographical coverage.
- Only tertiary hospitals were included, which might have led to population selection bias.
- Diagnosis of major NCDs was based on the ICD-10 coding with low sensitivity.
- Data of eGFR or proteinuria and information on medications were not available.

Background

There is a rising burden of non-communicable diseases (NCDs) at a global level. Two of three deaths each year are attributable to NCDs, and four-fifths of NCD-related deaths occur in low- and middle-income countries.[1] This exerts a significant influence on healthcare system and costs worldwide.[2] Taking action against NCDs is, therefore, an economic imperative.[3] The priority actions for the NCD crisis were released by the United Nations High-Level Meeting in 2011, focusing on the prevention and control of heart disease, stroke, cancer, diabetes, and chronic respiratory diseases.[1] The world leaders also committed to reduce premature deaths from NCDs by one-third by 2030.[3]

Over the past decade, chronic kidney disease (CKD) has been recognized as a major public health issue worldwide, with an estimated prevalence of more than 10%.[4 5] By 2040, CKD is estimated to become the fifth leading cause of early death globally—one of the largest projected increases of any major cause of death.[6] In China, CKD is prevalent and is associated with more severe comorbidities and higher medical expenditures.[7 8] However, unlike other NCDs, such as diabetes, the awareness of CKD is low among patients and healthcare providers.[9] Besides, CKD is a key determinant of poor health outcomes of major NCDs and a risk multiplier in patients with cardiovascular disease (CVD), diabetes, and hypertension.[10] Due to the fact that the kidneys are usually target organs of systemic vascular, hemodynamic, metabolic, and inflammatory disorders, the pandemic of NCDs also leads to a persistently increasing morbidity of CKD.[11] There is accumulating evidence that major NCDs, including heart disease and stroke, have a poor prognosis in the presence of CKD.[12-14] Moreover, CKD has been reported to be associated with reduced implementation of best clinical practice, which could lead to suboptimal

treatment and adverse outcomes, especially for patients with CVD.[15]

Although CKD is a global health issue, to the best of our knowledge, there have been neither large-scale studies to quantitatively evaluate the burden of CKD on all major NCDs, nor studies comparing the burden of CKD with other NCDs. The evidence for the impacts of CKD and other major NCDs on the healthcare system at a national level is limited, which impedes the development of effective preventive strategies. In addition, little is known about the status of cardiac procedures for patients with CKD in China. Hence, we initiated this observational study to comprehensively and quantitatively evaluate the impact of CKD on healthcare resource utilization and prognosis of other NCDs, as well as to compare the burden of kidney diseases on the healthcare system with other NCDs among hospitalized patients in China.

Methods

Study population

The Hospital Quality Monitoring System (HQMS) is a mandatory patient-level national database for hospital accreditation under the authority of the National Health Commission of the People's Republic of China. Details of HQMS have been described elsewhere.[16 17] In brief, all tertiary hospitals in China have been requested to submit electronic inpatient discharge records to HQMS on a daily basis. Unlike the Western medical system, tertiary hospitals in China provide primary, secondary, and tertiary care and have exposure to nationwide patient population. Patient-level data were collected from uniform front pages of hospitalization medical records. Altogether 353 variables including demographic characteristics, clinical diagnoses, procedures, pathology

diagnoses, and expenditure breakdowns were collected. All personal information has already been de-identified to protect patient privacy. The diagnoses were coded based on the International Classification of Diseases-10 (ICD-10) coding system by certified professional medical coders at every hospital. As the part of stringent standard practice in China, the front page has the legal validity and must be filed by the care-giving doctors who have the most accurate and comprehensive understanding of the patient's medical condition.

A total of 19,518,990 records of adult inpatients admitted from July 1, 2013 to June 30, 2014 in 29 provinces (excluding Hong Kong, Macao, Taiwan, Tibet, and Ningxia) were included in this cross-sectional study, with certain patients having more than one hospitalization. During this period, 715 tertiary hospitals in China, accounting for 44% of all tertiary hospitals in the country, had submitted inpatient records to HQMS database. Hospitalizations were used in the present analysis since they are more relevant to the discussion of "disease burden".[18] This study was approved by the Ethics Committee of Peking University First Hospital (2015-928) and informed consent was waived by the Ethics Committee.

Definition of CKD

The ICD-10 coding of discharge diagnoses was used to identify patients with CKD.[16 17] Hospitalizations of patients with at least one of the following diagnoses (in both primary diagnosis and secondary diagnoses) were identified as having CKD (relevant ICD-10 coding in supplemental Appendix 1): glomerulonephritis, diabetic nephropathy, hypertensive nephropathy, obstructive nephropathy, renal cancer, tubulointerstitial

nephritis, kidney disease secondary to autoimmune diseases, kidney failure of unknown reason. Among patients' records with CKD, only 14% of them had the information on CKD staging.

Validation study

Since the laboratory results are not included in the HQMS dataset, we performed a validation study using 67,376 hospitalizations in three hospitals in the HQMS. Those were the pilot hospitals that accomplished the HQMS phase 2 data collection expansion to the data of laboratory tests and medications.[19] The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) Study equation tailored for Chinese CKD patients.[20] Proteinuria was defined by urinary albumin-to-creatinine ratio (ACR) ≥30 mg/g creatinine, and/or urinary protein ≥trace in urine routine test. CKD was defined as the presence of proteinuria and/or eGFR less than 60 ml/min/1.73 m^2. Compared with the gold standard, the sensitivity and specificity of CKD identification by ICD-10 coding was 34.2% and 97.8%, respectively.[19]

Definition of other NCDs

Major NCDs, including coronary heart disease (CHD), stroke, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), and cancer,[1] were identified by the ICD-10 coding of hospital discharge diagnoses (in both primary and secondary diagnoses, relevant ICD-10 coding in supplemental Appendix 1). Information on coronary angiography (CAG), percutaneous coronary intervention (PCI), and coronary artery

bypass grafting was obtained from the procedure coding of the front page for patients with CHD. For patients with multiple NCD diagnoses, each relevant diagnosis was identified and counted when stratified by the above NCDs.

Other covariates

Individual variables including age, sex, occupation (professional, worker, farmer, retired, unemployed, and others), type of health insurance (basic medical insurance, new rural cooperative medical care, other types of insurance, and uninsured), type of admission (emergency, routine, and others), and intensive care unit (ICU) stay were collected from the front page.

Outcomes

Hospitalization costs and length of hospital stay, which are both important indicators for healthcare resource utilization, were acquired from the front page. The total costs of the patient's hospitalization were jointly borne by the patient, the government, and related insurers, and included costs for prescribed drugs, hospital beds, laboratory tests, medical examinations, and surgical costs. Information on in-hospital mortality was also collected to assess the prognosis of patients. The survival status of each patient was verified based on the discharge status and combined with the information of autopsy.

Statistical analysis

General characteristics stratified by the presence of CKD for each NCD were described. Continuous data were presented as mean ± standard deviation, or as median (interquartile

range) for highly skewed variables. Categorical variables were presented as proportions. All of the analyses were based on the hospitalizations (patient records), not individuals.

The effects of CKD on healthcare resource utilization for each NCD were analyzed using generalized linear regression models for log-transformed cost and length of stay. Poisson regression model was used to evaluate the impacts of CKD and other NCDs on in-hospital mortality. Percent of change and relative risk (RR) with 95% confidence interval (CI) were reported and calculated as exp(β)–1 and exp(β), respectively. For the purpose of assessing additional effects of CKD, covariates included in the model for the sub-dataset of each NCD were age (5-year categories, except for 18–25 years and >80 years), sex (male vs. female), type of health insurance (dummy variable), type of admission (dummy variable), ICU stay (yes vs. no), presence of CKD (yes vs. no), presence of other NCDs (yes vs. no), pneumonia (yes vs. no), and sepsis (yes vs. no).

Then, the presence of CKD and other NCDs was included in the models simultaneously, using the data of all hospitalized patients, in order to compare the effect of CKD with that of other NCDs on outcome variables. Similar covariates were used as described previously.

For hospitalized patients with CHD, percentages of those with CAG and PCI were reported among different clinical types (including ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, and non-acute coronary syndrome), stratified by the presence of CKD. Among 18,315 hospitalizations with CHD and with available CKD staging, the percentages of those with CAG and PCI were also reported.

The sensitivity analysis was conducted among patients with CKD stages 3-5 to

further determine the impacts of CKD on healthcare resource utilization (Appendices 2 and 3). All analyses were performed using the SAS software, version 9.4 (SAS Institute Inc, Cary, NC). Due to the large sample size of our study, *P* values were not reported for between-group comparisons.

Patient and public involvement statement

Patients or the public were not involved in this study.

Results

Among 19.5 million hospitalizations, the percentages of diagnosed CKD, CHD, stroke, hypertension, diabetes, COPD, and cancer were 4.5%, 9.2%, 8.2%, 18.8%, 7.9%, 2.3%, and 19.4%, respectively (table 1). For each major NCD, individuals with CKD were older (except for hypertension); were more often male and urban residents; more often stayed in ICU and had infectious diseases such as pneumonia and sepsis (except for COPD).

For each major NCD, the presence of CKD was independently associated with longer hospital stay, with increased percentages ranging from 7.69% (95% CI, 7.11%–8.28%, for stroke) to 21.60% (95% CI, 21.09%–22.10%, for CHD) (Table 2). After adjusting for potential confounders, the presence of CKD was associated with higher costs for stroke (11.15%; 95% CI, 10.31%–11.99%), COPD (19.46%; 95% CI, 17.97%–20.97%), and cancer (18.88%; 95% CI, 17.98%–19.78%). In contrast, the costs were slightly lower for CHD (acute coronary syndrome or non-acute coronary syndrome) (−1.08%; 95% CI, −1.71% to −0.45%), hypertension (−0.22%; 95% CI, −0.60% to 0.16%), and diabetes (−0.97%; 95% CI, −1.43% to –0.51%) in the presence of CKD

(Table 2). If patients with CHD were excluded, the presence of CKD was associated with increased costs for patients with hypertension and diabetes, with a fully adjusted change of 2.70% (95% CI, 2.24%–3.15%) and 4.11% (95% CI, 3.56%–4.66%), respectively. The in-hospital mortality was also higher in the presence of CKD for major NCDs, with fully adjusted RR ranging from 1.91 (95% CI, 1.82–1.99, for stroke; 95% CI, 1.85–1.97, for hypertension) to 2.65 (95% CI, 2.55–2.75, for cancer) (Table 2).

Among hospitalizations with CHD, the percentages of individuals with CAG and PCI were substantially lower for those with CKD (Figure 1). A similar pattern was observed for coronary artery bypass grafting, which was 0.3% and 1.0% for CHD patients with or without CKD, respectively. Even for those with acute coronary syndrome or cardiogenic shock—a strong indication for emergency PCI[21]—the trend was still similar: 11.9% vs. 22.2% for ST-elevated myocardial infarction, and 3.5% vs. 7.3% for non-ST elevated myocardial infarction. Furthermore, among hospitalizations with available CKD staging and with CHD, the percentages of individuals with CAG and PCI were lower even for stage 1 and 2, compared with those without CKD and with CHD (Figure 1).

Compared with other NCDs, CKD had the highest increase in length of hospital stay (22.09%; 95% CI, 21.87%–22.32%) (Table 3). Cancer and CHD were associated with the highest contribution to increased costs for hospitalized patients, which was 39.47% (95% CI, 39.29%–39.65%) and 30.95% (95% CI, 30.71%–31.19%), respectively. CKD was associated with 6.82% (95% CI, 6.56%–7.08%) increased costs. Furthermore, CKD resulted in the second highest in-hospital mortality (RR, 2.23; 95% CI, 2.19–2.28), which was only lower than that of cancer (RR, 2.87; 95% CI, 2.83–2.91).

Discussion

This study is the first national quantitative study on the burden of CKD and other major NCDs and their impacts on the healthcare system in China. The findings of this study indicated that the presence of CKD was associated with additional burden on the healthcare system and increased in-hospital mortality for each major NCD, despite evidence of under-utilization of cardiac procedures in the presence of CKD. Furthermore, the impacts of CKD on healthcare resource utilization and mortality were comparable to those of other major NCDs in this large national sample of 19.5 million hospitalizations.

Studies regarding the utilization of healthcare resources for CKD mostly focused on end-stage kidney disease (ESKD).[22-24] The US Renal Data System 2019 Annual Data Report showed that the costs for both CKD and ESKD were in excess of $120 billion in 2017, and the latter accounted for more than 7.2% of the total Medicare expenditure.[25] Our study revealed that CKD was associated with a 6.8% increase in costs, which was higher than that of hypertension, diabetes, and COPD. Moreover, for each major NCD, the presence of CKD led to longer hospital stay, which is also an important marker for healthcare resource utilization. Furthermore, considering the evidence of therapeutic nihilism for patients with CKD (documented for cardiac revascularization) and the insensitivity of diagnostic codes for CKD, the impacts of CKD on the healthcare system might be underestimated. A recent systematic review has also shown that the risks of adverse cardiovascular outcomes increase with CKD and are associated with substantial additional costs and resource utilization.[26]

Several previous studies have reported that both the general and high-risk

populations have poor prognoses in the presence of kidney diseases. For example, using the data of 1.1 million adults within a large integrated healthcare system, Go *et al*. observed increased risks of all-cause mortality, CVD, and hospitalization associated with reduced kidney function.[12] A recent meta-analysis has reported that both reduced eGFR and elevated urinary albumin-to-creatinine ratio are associated with increased all-cause and cardiovascular mortality in the general population.[27] Similarly, using data from over 40 cohorts involving one million participants, it has been reported that the adjusted hazard ratio for all-cause mortality at an eGFR of 45 ml/min/1.73 m^2 was 1.24 (95% CI, 1.11–1.39) for those with hypertension,[28] and was 1.35 (95% CI 1.18–1.55) for those with diabetes,[29] compared with those with eGFR of 95 ml/min/1.73 m^2. In this study, we further expanded the observation to a range of other major NCDs, including CHD, stroke, COPD, and cancer. We found that CKD was consistently associated with increased in-hospital mortality for each major NCD, and its impact was higher compared with that of the majority of NCDs, even comparable to that of cancer. These findings further highlight the importance of CKD as a major health burden and are consistent with the implications of Global Burden of Disease, Injuries, and Risk Factors Study, which has shown the high burden and rapid growth of CKD as a direct cause of morbidity and mortality.[4 6]

The potential mechanisms for the association of CKD and adverse outcomes are complex and not fully understood. A previous study indicated that impaired kidney function could lead to multiple adverse systemic alterations, including inappropriate activation of the renin-angiotensin system, catalytic iron-dependent oxidative stress, endothelial dysfunction, and inflammation.[14] In addition, for patients whose CKD is a result of a systemic disease such as diabetes, kidney diseases might only serve as a

marker of the severity of the target organ damage.

Another explanation for the adverse outcomes observed in patients with CKD might be that the presence of CKD is associated with reduced implementation of best practice. Although the accumulating evidence and the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines with international consensus suggest that the level of care for ischemic heart disease offered to patients with CKD should not be prejudiced by their CKD,[30] our data on revascularization indicate that cardiac treatment for patients with CKD is suboptimal. Under-utilization of aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, glycoprotein IIb/IIIa receptor antagonists, and thrombolytic therapy has been observed in CKD patients due to concerns of bleeding risk, worsening of kidney function, and comorbidities.[15] A recent study from the United States indicated that, compared with those without CKD, patients with CKD reported more medication use for cardiovascular risk factors but had poorer risk factor control.[31] In our study, the percentages of hospitalizations with CAG and PCI were much lower for those with CKD, even for those with relatively well-preserved kidney function, consistent with the practice outside of China.[15] A recent meta-analysis has revealed that for patients with pre-dialysis CKD and with unstable angina or non-ST-segment-elevation myocardial infarction, an early invasive strategy is associated with the risk of re-hospitalization and reduced risk of death and non-fatal re-infarction.[32] However, the risk of adverse clinical events after coronary revascularization and the percentage of later additional PCI are also increased in patients with CKD.[33 34] Hence, a multidisciplinary team involving various subspecialties is needed to improve the quality of care for CKD patients, and appropriate management by primary care clinicians is necessary to prevent CKD-associated adverse outcomes.[35]

To our knowledge, this is the first study that places the CKD burden on hospital stay and mortality in the full context of all major NCDs in a national database with large sample size and wide geographical coverage, which enables us to analyze the impacts of multiple major NCDs simultaneously. However, our study does have some limitations. First, although our data were restricted to hospitalized patients, hospitalization inherently reflects indication for admission and referral as well as disease burden. Only tertiary hospitals were included in our analyses, which might have led to population selection bias; nevertheless, 715 hospitals in our study covered almost all provinces of China and included all types of tertiary hospitals. Second, the diagnosis of CKD and major NCDs in hospitalized patients was based on the ICD-10 coding, which has low sensitivity. Severe cases of CKD were likely to be diagnosed, which might affect the extrapolation of the results and lead to a potential overestimation of the excess risk associated with CKD. However, the high specificity of CKD identification (97.8%) is the strength of our study. Third, the low usage of CKD-staging codes was a limitation that should be recognized. Further evaluation of the healthcare utilization in different CKD stages is worthwhile. Fourth, since hospitalizations were identified using both primary and secondary diagnoses, the direct contribution of specific NCDs to health resource utilization might have been compromised. All of the analyses were based on the hospitalizations, and cases reported in the results were not mutually exclusive, which may also affect the estimations of the true burden of disease. Finally, data on eGFR or proteinuria and information on medications used and the severity of major NCDs were not available for all patient records in our dataset.

Conclusions

In a systematic national assessment of diagnosed NCDs over 19.5 million hospitalizations in China, we showed that the adverse effects of CKD at both individual level and healthcare system level were comparable to those of other major NCDs, and the presence of CKD was associated with poor prognosis of other NCDs. Therefore, CKD should be integrated into the global prevention strategy of NCDs. In consideration of the complexity of the disease, a multilevel interdisciplinary approach will be needed to address the public health burden of CKD.

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Contributors

HW and LZ conceived and coordinated the study and acquired the data. CY, HW, and LZ designed the study. CY and LZ searched the literature. CY and JL prepared the figure. CY, HW, and LZ wrote the first draft manuscript. CY, JL, SY, and ZZ contributed to the analysis. CY, JL, SY, ZZ, JW, M-HZ, HW, LZ, and JC contributed to the interpretation. CY, JL, SY, ZZ, JW, M-HZ, HW, LZ, and JC edited the manuscript. All authors critically reviewed the manuscript and approved the final version.

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Competing interests

JC was partly supported by grants to the CKD Prognosis Consortium by the National Kidney Foundation and NIH.

Patient and public involvement statement

Patients or the public were not involved in this study.

Patient consent for publication

Not required.

Ethics approval

Ethical approval was obtained from the Ethics Committee of Peking University First Hospital (2015-928).

Data availability statement

The data that support the findings of this study are available from the Bureau of Medical Administration and Medical Service Supervision, National Health Commission of China but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Bureau of Medical Administration and Medical Service Supervision, National Health Commission of China.

Supplementary material

Appendix 1. The International Classification of Diseases-10 coding of chronic kidney disease and other major non-communicable chronic diseases

Appendix 2. Effects of chronic kidney disease stages 3-5 on length of stay, costs, and in-hospital mortality for each non-communicable disease

Appendix 3. Effects of chronic kidney disease stages 3-5 on length of stay, costs, and in-hospital mortality, compared with other major non-communicable diseases

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Figure 1. Percentages of hospitalizations with coronary angiography and percutaneous coronary intervention for individuals with coronary heart disease

Note: The number of hospitalizations with or without CKD was 3,116 and 68,616 for STEMI, respectively; 2,645 and 25,057 for NSTEMI, respectively; and 124,388 and 1,519,864 for NACS, respectively. For 18,315 hospitalizations with available CKD staging, 15.8%, 24.6%, 16.8%, and 42.9% of individuals were in stages 1–2, 3, 4, and 5, respectively.

Abbreviations: CKD, chronic kidney disease; NACS, non-acute coronary syndrome; NSTEMI, non-ST-segment-elevation myocardial infarction; STEMI, ST-segment-elevation myocardial infarction.

Table 1. Characteristics of hospitalized patients with non-communicable chronic diseases stratified by the presence of chronic kidney disease

	CHD		Stroke		Hypertension		Diabetes		COPD		Cancer		Total	
	CKD	Non-CKD	CKD	Non-CKD	CKD	Non-CKD	CKD	Non-CKD	CKD	Non-CKD	CKD	Non-CKD	CKD	Non-CKD
Number	132032	1665601	79 906	1529843	348075	3322665	222157	1321816	22998	429475	22585	3698423	871742	18647248
Percentage (%)	0.7	8.5	0.4	7.8	1.8	17.0	1.1	6.8	0.1	2.2	0.4	19.0	4.5	95.5
Main outcomes														
Costs (1000 yuan)	11 (7-20)	9 (6-20)	11 (7-19)	9 (6-16)	10 (6-17)	9 (6-16)	10 (7-16)	9 (6-16)	12 (8-22)	10 (6-16)	17 (7-29)	10 (6-20)	9 (6-17)	8 (4-14)
Length of stay (days) †	11 (8-17)	9 (6-13)	12 (8-17)	11 (7-15)	11 (7-16)	9 (6-14)	12 (8-16)	10 (7-14)	12 (8-19)	10 (7-15)	11 (7-19)	8 (4-14)	11 (6-16)	8 (5-13)
Mortality (%)	3.5	1.4	3.5	1.5	1.8	0.9	1.8	0.9	4.9	1.9	5.0	1.0	1.8	0.6
Demographic characteristics														
Age (years)	71.4±11.8	68.1±12.0	69.1±13.0	65.9±12.9	64.7±14.3	65.7±12.3	63.7±13.2	63.3±12.8	76.7±9.6	72.8±10.3	62.1±13.8	56.7±13.3	57.7±17.0	52.7±17.6
Male (%)	60.2	55.4	62.6	55.1	59.4	52.2	57.6	53.1	76.6	71.7	63.4	49.7	57.3	45.6
Occupation (%)†														
Professional	7.6	8.7	8.0	8.5	9.8	9.2	11.0	11.2	4.2	4.2	10.4	11.1	11.9	14.4
Worker	4.9	5.3	5.6	5.9	5.9	5.9	6.5	6.3	3.8	4.7	6.2	6.2	6.6	7.1
Farmer	11.8	18.1	15.7	23.0	15.6	19.1	14.7	15.8	15.2	23.2	17.6	24.7	21.3	21.5
Retired	40.9	32.4	36.6	27.7	30.6	28.7	31.0	28.3	42.3	31.3	25.3	14.5	20.7	13.8
Unemployed	7.0	6.3	7.1	7.4	8.6	7.3	8.7	7.4	7.5	7.8	8.6	9.7	9.4	10.1
Others	27.8	29.4	27.0	27.4	29.5	29.9	28.2	31.1	27.1	28.9	31.9	33.7	30.2	33.1
Health insurance (%)														
Basic medical insurance	66.0	59.0	62.7	54.0	59.6	57.0	62.3	59.9	63.1	54.3	71.2	43.0	49.9	42.9
NRCMC	12.5	18.7	15.8	22.6	16.9	19.4	15.8	16.7	15.5	24.4	9.8	26.7	23.2	22.5
Others	11.0	11.6	9.8	10.3	10.6	10.3	9.9	10.3	10.2	10.0	13.6	12.7	11.4	13.0
Uninsured	10.5	10.8	11.8	13.1	12.9	13.3	12.0	13.1	11.2	11.3	5.5	17.6	15.4	21.6
Admission and comorbidity information														
Admission (%)†														
Emergency	21.6	22.6	25.3	29.3	17.3	20.5	16.5	16.9	22.9	23.1	10.8	7.4	16.1	17.9
Routine	71.6	69.4	68.3	63.2	76.0	72.2	76.6	75.1	69.1	68.9	80.1	82.4	76.0	72.6
Others	6.8	7.9	6.5	7.6	6.7	7.4	6.9	8.0	8.0	8.0	9.2	10.2	7.9	9.5
ICU stay (%)	4.1	3.0	3.9	2.7	2.4	2.0	2.2	1.7	5.1	3.2	2.0	0.7	2.0	1.2
Hypertension (%)	69.6	55.3	71.1	56.6	--	--	62.7	52.6	54.8	33.6	32.3	12.2	39.9	17.8
CHD (%)	--	--	28.2	18.7	26.4	27.7	26.8	25.8	35.9	23.0	9.4	2.9	15.2	8.9
Stroke (%)	17.1	17.1	--	--	16.3	26.0	14.8	18.9	12.7	9.5	4.8	1.8	9.2	8.2
COPD (%)	6.2	5.9	3.7	2.7	3.6	4.3	2.6	3.1	--	--	2.2	1.1	2.6	2.3
Cancer (%)	5.7	6.5	4.9	4.4	7.5	13.5	5.0	13.4	7.9	9.6	--	--	9.2	19.8

Diabetes (%)	45.0	20.5	41.2	16.3	40.0	20.9	--	--	24.6	9.6	33.7	4.8	25.5	7.1
Pneumonia (%)	6.1	4.1	5.8	3.6	4.3	3.6	4.3	3.4	8.3	8.5	7.7	2.0	3.7	2.3
Sepsis (%)	0.5	0.2	0.7	0.2	0.5	0.2	0.7	0.3	0.7	0.3	0.6	0.2	0.6	0.2

[†]The percentages of missing values for occupation, type of admission, and length of stay were 10.9%, 6.4%, and 16.6% for CHD; 10.5%, 7.1%, and 17.5% for stroke; 10.7%, 6.7%, and 16.2% for hypertension; 10.7%, 6.9%, and 16.6% for diabetes; 12.2%, 5.4%, and 18.0% for COPD; and 11.4%, 6.1%, and 15.2% for cancer.

Abbreviations: CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; NCDs, non-communicable chronic diseases; NRCMC, New Rural Cooperative Medical Care.

Table 2. Effects of chronic kidney disease on length of stay, costs, and in-hospital mortality for each non-communicable disease

Condition	Covariates in the model	Length of stay % change (95% CI)	Costs % change (95% CI)	In-hospital mortality relative risk (95% CI)
CHD	Model 1	24.58 (24.1, 25.06)	4.96 (4.34, 5.58)	2.15 (2.08, 2.22)
	Model 2	21.99 (21.49, 22.5)	−0.26 (−0.90, 0.37)	2.09 (2.02, 2.16)
	Model 3	21.60 (21.09, 22.10)	−1.08 (−1.71, −0.45)	2.02 (1.95, 2.09)
Stroke	Model 1	11.35 (10.80, 11.90)	16.65 (15.81, 17.49)	2.17 (2.08, 2.26)
	Model 2	8.26 (7.68, 8.85)	13.05 (12.19, 13.91)	2.01 (1.92, 2.10)
	Model 3	7.69 (7.11, 8.28)	11.15 (10.31, 11.99)	1.91 (1.82, 1.99)
Hypertension	Model 1	14.46 (14.17, 14.74)	−0.40 (−0.76, −0.04)	1.94 (1.89, 2.00)
	Model 2	16.24 (15.92, 16.55)	0.49 (0.10, 0.87)	1.97 (1.91, 2.03)
	Model 3	16.01 (15.70, 16.33)	−0.22 (−0.60, 0.16)	1.91 (1.85, 1.97)
Diabetes	Model 1	14.05 (13.70, 14.41)	−2.90 (−3.33, −2.47)	1.88 (1.82, 1.95)
	Model 2	16.55 (16.16, 16.94)	−0.14 (−0.60, 0.33)	2.02 (1.94, 2.10)
	Model 3	16.32 (15.93, 16.70)	−0.97 (−1.43, −0.51)	1.95 (1.88, 2.03)
COPD	Model 1	15.85 (14.84, 16.87)	31.41 (29.78, 33.06)	2.21 (2.08, 2.35)
	Model 2	11.14 (10.11, 12.18)	20.15 (18.65, 21.68)	1.99 (1.86, 2.13)
	Model 3	11.05 (10.02, 12.09)	19.46 (17.97, 20.97)	1.97 (1.84, 2.11)
Cancer	Model 1	21.38 (20.66, 22.11)	25.84 (24.96, 26.72)	3.30 (3.19, 3.41)
	Model 2	17.87 (17.11, 18.64)	19.63 (18.72, 20.54)	2.75 (2.65, 2.85)
	Model 3	17.50 (16.74, 18.26)	18.88 (17.98, 19.78)	2.65 (2.55, 2.75)

Note: Numbers in the table are percent-changes/relative risks of patient records with CKD compared with patient records without CKD for each non-communicable disease.

Covariates in model 1 included age and sex.

Covariates in model 2 included age, sex, occupation, type of health insurance, type of admission, intensive care unit stay, presence of CHD, stroke, hypertension, diabetes, COPD, and cancer (except for the disease used to define the subgroup).

Covariates in model 3 included covariates in model 2, plus the presence of sepsis and pneumonia.

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

Table 3. Effects of chronic kidney disease on length of stay, costs, and in-hospital mortality, compared with other major non-communicable diseases

Condition	Covariates in the model	Length of stay % change (95% CI)	Costs % change (95% CI)	In-hospital mortality relative risk (95% CI)
CKD	Model 1	22.34 (22.14, 22.55)	6.49 (6.25, 6.73)	2.31 (2.27, 2.35)
	Model 2	22.09 (21.87, 22.32)	6.82 (6.56, 7.08)	2.23 (2.19, 2.28)
CHD	Model 1	−5.19 (−5.31, −5.07)	27.72 (27.51, 27.94)	1.36 (1.34, 1.38)
	Model 2	−7.31 (−7.44, −7.18)	30.95 (30.71, 31.19)	1.31 (1.29, 1.33)
Stroke	Model 1	16.12 (15.97, 16.27)	9.29 (9.10, 9.48)	1.58 (1.56, 1.60)
	Model 2	17.34 (17.17, 17.51)	9.90 (9.69, 10.11)	1.70 (1.67, 1.73)
Hypertension	Model 1	5.49 (5.39, 5.59)	8.90 (8.77, 9.04)	0.93 (0.92, 0.94)
	Model 2	1.81 (1.69, 1.92)	4.85 (4.70, 5.01)	0.76 (0.75, 0.77)
Diabetes	Model 1	11.36 (11.22, 11.51)	5.05 (4.87, 5.23)	1.13 (1.11, 1.15)
	Model 2	8.96 (8.80, 9.12)	1.00 (0.81, 1.20)	0.99 (0.97, 1.01)
COPD	Model 1	3.89 (3.65, 4.14)	−9.00 (−9.29, −8.71)	1.31 (1.28, 1.34)
	Model 2	5.77 (5.50, 6.04)	−8.67 (−8.98, −8.36)	1.24 (1.21, 1.27)
Cancer	Model 1	8.90 (8.80, 9.00)	27.40 (27.25, 27.55)	2.00 (1.97, 2.02)
	Model 2	13.90 (13.79, 14.02)	39.47 (39.29, 39.65)	2.87 (2.83, 2.91)

Note: Numbers in the table are percent-changes/relative risks of patient records with corresponding disease compared with patient records without corresponding disease.

Covariates in model 1 included age and sex.

Covariates in model 2 included age, sex, occupation, type of health insurance, type of admission, intensive care unit stay, presence of CKD, CHD, stroke, hypertension, diabetes, COPD, and cancer, and presence of sepsis and pneumonia.

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

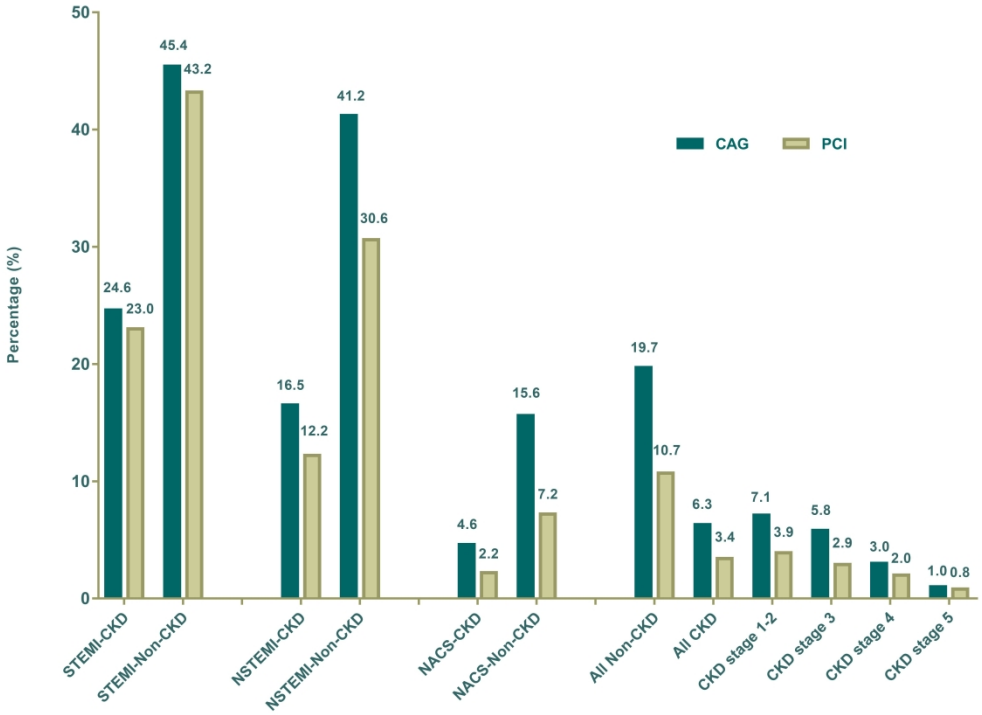

Figure 1. Percentages of coronary angiography and percutaneous coronary intervention for hospitalizations with coronary heart disease

Note: The number of hospitalizations with or without CKD was 3,116 and 68,616 for STEMI, 2,645 and 25,057 for NSTEMI, 124,388 and 1,519,864 for NACS, respectively. For 18,315 hospitalizations with diagnoses of CKD staging, 15.8%, 24.6%, 16.8%, and 42.9% of them were in stage 1-2, 3, 4 and 5.

Abbreviations: CKD, chronic kidney disease; NACS, non-acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

227x170mm (600 x 600 DPI)

Appendix 1. The International Classification of Diseases-10 coding of chronic kidney disease and other major non-communicable chronic diseases

Disease		ICD-10 coding
CKD		E10.2+, E11.2+, E13.2+, E14.2+, I12.0, I12.9, I13.0, I13.1, I13.2, I13.9, N11, N12, N14, N15, N16.*, E74.8, E72.0, N25.1, M32.1+N08.5*, M32.1+N16.4*, M35.0+N16.4*, M31.0+N08.5*, M31.7+N08.5*, M31.001‡, M31.802‡, M32.101+N08.5*†, M31.102+N08.5*†, M31.303+N08.5*†, N18, N19, N13.0, N13.1, N13.2, C64, N07, N08 (excluding N08.5*), N13.6, Q60, Q61.1, Q61.2, Q61.3, Q61.5, Q63.1, Q63.9, M10.3, N26, N28.8, N28.8, N28.9, A52.7+N08.0*, N99.0, P96.0, R39.2, K76.7, Q27.1, I70.1, M31.4 (combined with I15.0) N00.8, N02, N03, N04, N05, N06, N39.1
CHD	CHD†	I21.001, I21.002, I21.004, I21.101, I21.103, I21.104, I21.105, I21.201, I21.202, I21.203, I21.204, I21.205, I21.206, I21.207, I21.208, I21.209, I21.210, I21.211, I21.213, I21.214, I21.215, I21.301, I21.302, I21.304, I21.907, I21.403, I24.003, I20.001, I20.002, I20.003, I20.004, I20.005, I20.006, I20.101, I20.102, I20.802, I20.803, I21.303, I21.401, I21.402, I21.901, I21.902, I21.910, I22.001, I22.101, I22.801, I22.802, I22.803, I22.901, I23.001, I23.002, I23.101, I23.201, I23.301, I24.001, I24.002, I24.003, I24.004, I24.005, I24.006, I24.101, I24.102, I24.801, I24.802, I24.901, I20.801, I20.804, I20.805, I20.806, I20.902, I25.103, I25.104, I25.105, I25.201, I25.202, I25.203, I25.204, I25.205, I25.206, I25.207, I25.208, I25.209, I25.210, I25.211, I25.212, I25.213, I25.214, I25.215, I25.501, I25.601, I25.901, I25.902
	CHD‡	I21.000, I21.001, I21.002, I21.003, I21.004, I21.005, I21.006, I21.007, I21.100, I21.101, I21.102, I21.103, I21.104, I21.105, I21.200, I21.201, I21.202, I21.203, I21.204, I21.205, I21.206, I21.300, I21.301, I21.401, I20.000, I20.001, I20.002, I20.003, I20.004, I20.005, I20.006, I20.100, I20.101, I20.102, I20.804, I21.302, I21.303, I21.400, I21.402, I21.900, I22.000, I22.100, I22.800, I22.900, I23.000, I23.100, I23.200, I23.300, I23.400, I23.500, I23.600, I23.601, I23.800, I24.000, I24.001, I24.100, I24.101, I24.800, I24.801, I24.900, I24.901, I20.801, I20.802, I20.803, I20.804, I20.900, I25.000, I25.100, I25.101, I25.102, I25.103, I25.500, I25.500, I25.600, I25.800, I25.801, I25.900, I25.901,
COPD		J44.901†, J44.003†, J44.103†, J44.900‡, J44.000‡, J44.100‡, J44.800‡
Stroke		I60, I61, I63, I64, G45, H34.1
Diabetes		E10, E11, E12, E13, E14
Cancer		C00-C26, C30-C34, C37-C41, C43-C58, C60-C85, C88, C90-C97, D00-D07, D09, D37-D48, B21, Z85, Z08 Z51.10†, Z51.20†, Z51.50†, Z03.101†, E87.805†, O99.8011†, O99.8021†, O99.8024†, O99.8031†, Z51.00‡, Z51.10‡, Z51.80‡, Z03.10‡, O99.802‡, Z35.802‡, Z54.001‡, E88.805‡, Z86.000‡
Hypertension		I10

Disease	ICD-10 coding
Sepsis	A41
Pneumonia	J12-J18

†Applicable for ICD-10 (Beijing Version 4.0) only.

‡Applicable for ICD-10 (National Standard Version1.0) only.

*Denotes to any possible number so that the whole sequence represents all the subclasses of the disease.

Abbreviations: CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary diseases. ICD-10, International Classification of Diseases-10.

Appendix 2. Effects of chronic kidney disease stages 3-5 on length of stay, costs, and in-hospital mortality for each non-communicable disease

Condition	Covariates in the model	Length of stay % change (95% CI)	Costs % change (95% CI)	In-hospital mortality relative risk (95% CI)
CHD	Model 1	36.67 (35.19, 38.17)	14.54 (12.64, 16.47)	1.90 (1.73, 2.08)
	Model 2	38.68 (37.07, 40.30)	6.22 (4.35, 8.13)	1.93 (1.76, 2.13)
	Model 3	38.41 (36.81, 40.03)	5.69 (3.83, 7.58)	1.93 (1.76, 2.13)
Stroke	Model 1	22.81 (20.89, 24.75)	30.39 (27.46, 33.38)	2.12 (1.88, 2.39)
	Model 2	21.76 (19.67, 23.88)	25.48 (22.49, 28.55)	1.92 (1.69, 2.19)
	Model 3	21.13 (19.05, 23.24)	23.60 (20.66, 26.60)	1.79 (1.58, 2.05)
Hypertension	Model 1	19.77 (19.01, 20.54)	0.62 (-0.29, 1.53)	1.60 (1.49, 1.72)
	Model 2	25.88 (25.02, 26.75)	4.10 (3.10, 5.11)	1.83 (1.69, 1.98)
	Model 3	25.69 (24.83, 26.55)	3.47 (2.48, 4.47)	1.76 (1.63, 1.91)
Diabetes	Model 1	23.75 (22.71, 24.80)	10.24 (8.92, 11.58)	1.91 (1.75, 2.09)
	Model 2	29.22 (28.06, 30.40)	13.22 (11.80, 14.65)	2.14 (1.95, 2.36)
	Model 3	29.06 (27.90, 30.23)	12.55 (11.15, 13.98)	2.13 (1.93, 2.34)
COPD	Model 1	14.97 (11.79, 18.25)	36.41 (31.07, 41.97)	1.70 (1.37, 2.12)
	Model 2	15.21 (11.75, 18.77)	22.93 (17.93, 28.14)	1.74 (1.38, 2.19)
	Model 3	15.38 (11.92, 18.95)	22.80 (17.83, 27.97)	1.72 (1.36, 2.16)
Cancer	Model 1	24.54 (21.36, 27.80)	20.65 (17.08, 24.34)	2.15 (1.86, 2.49)
	Model 2	20.58 (17.23, 24.02)	12.13 (8.53, 15.85)	1.68 (1.44, 1.95)
	Model 3	19.72 (16.40, 23.14)	11.26 (7.70, 14.94)	1.49 (1.28, 1.73)

Note: Numbers in the table are percent-changes/relative risks of patient records with CKD compared with patient records without CKD

for each non-communicable disease. Covariates in model 1 included age and sex.

Covariates in model 2 included age, sex, occupation, type of health insurance, type of admission, intensive care unit stay, presence of CHD, stroke, hypertension, diabetes, COPD, and cancer (except for the disease used to define the subgroup).

Covariates in model 3 included covariates in model 2, plus the presence of sepsis and pneumonia.

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

Appendix 3. Effects of chronic kidney disease stages 3-5 on length of stay, costs, and in-hospital mortality, compared with other major non-communicable diseases

Condition	Covariates in the model	Length of stay % change (95% CI)	Costs % change (95% CI)	In-hospital mortality relative risk (95% CI)
CKD	Model 1	32.02 (31.40, 32.65)	14.97 (14.26, 15.70)	1.76 (1.67, 1.85)
	Model 2	35.61 (34.93, 36.30)	19.65 (18.86, 20.45)	1.92 (1.82, 2.02)
CHD	Model 1	-5.95 (-6.08, -5.83)	28.00 (27.78, 28.22)	1.34 (1.32, 1.36)
	Model 2	-7.67 (-7.80, -7.53)	31.31 (31.06, 31.56)	1.32 (1.29, 1.34)
Stroke	Model 1	16.71 (16.55, 16.86)	9.00 (8.81, 9.20)	1.62 (1.60, 1.65)
	Model 2	17.76 (17.59, 17.94)	9.58 (9.37, 9.80)	1.74 (1.71, 1.77)
Hypertension	Model 1	5.07 (4.97, 5.18)	9.26 (9.11, 9.40)	0.92 (0.91, 0.93)
	Model 2	2.15 (2.03, 2.26)	5.11 (4.95, 5.27)	0.78 (0.76, 0.79)
Diabetes	Model 1	10.38 (10.23, 10.53)	5.90 (5.70, 6.10)	1.09 (1.07, 1.11)
	Model 2	9.54 (9.37, 9.71)	1.90 (1.69, 2.11)	1.03 (1.01, 1.05)
COPD	Model 1	3.99 (3.74, 4.24)	-9.96 (-10.25, -9.67)	1.32 (1.29, 1.35)
	Model 2	5.83 (5.56, 6.11)	-9.48 (-9.80, -9.17)	1.24 (1.21, 1.27)
Cancer	Model 1	9.51 (9.41, 9.60)	26.96 (26.80, 27.11)	2.00 (1.98, 2.03)
	Model 2	14.07 (13.95, 14.18)	38.95 (38.76, 39.13)	2.87 (2.82, 2.91)

Note: Numbers in the table are percent-changes/relative risks of patient records with corresponding disease compared with patient records without

corresponding disease.

Covariates in model 1 included age and sex.

Covariates in model 2 included age, sex, occupation, type of health insurance, type of admission, intensive care unit stay, presence of CKD, CHD, stroke, hypertension, diabetes, COPD, and cancer, and presence of sepsis and pneumonia.

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-10
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	10
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	-
Outcome data	15*	Report numbers of outcome events or summary measures	11-13

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	11-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Healthcare resource utilization of chronic kidney disease and other major non-communicable chronic diseases in China: a cross-sectional study

Running head: CKD and NCDs in China

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Abstract

Objective: To evaluate the healthcare resource utilization of chronic kidney disease (CKD) and other major non-communicable chronic diseases (NCDs) in China.

Design: A cross-sectional study.

Setting: A national inpatient database of tertiary hospitals in China.

Participants: A total of 19.5 million hospitalizations of adult patients from July, 2013 to June, 2014. Information on CKD and other major NCDs, including coronary heart disease (CHD), stroke, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), and cancer was extracted from the unified discharge summary form.

Outcome measures: Costs, length of hospital stay, and in-hospital mortality.

Results: The percentages of hospitalizations with CKD, CHD, stroke, hypertension, diabetes, COPD, and cancer were 4.5%, 9.2%, 8.2%, 18.8%, 7.9%, 2.3%, and 19.4%, respectively. For each major NCD, the presence of CKD was independently associated with longer hospital stay, with increased percentages ranging from 7.69% (95% confidence interval [CI], 7.11%–8.28%) for stroke to 21.60% (95% CI, 21.09%–22.10%) for CHD. The hospital mortality for other NCDs was also higher in the presence of CKD, with fully adjusted relative risk ranging from 1.91 (95% CI, 1.82–1.99) for stroke to 2.65 (95% CI, 2.55–2.75) for cancer. Compared with other NCDs, CKD was associated with the longest hospital stay (22.1% increase) and resulted in the second highest in-hospital mortality, only lower than that of cancer (relative risk, 2.23 vs. 2.87, respectively).

Conclusions: The presence of diagnosed CKD alongside each major NCD was associated with an additional burden on the healthcare system. The healthcare resource utilization and prognosis of CKD were comparable to those of other major NCDs, which

highlights the importance of CKD as a major public health burden.

Keywords

Chronic kidney disease; Disease burden; Health care costs; Length of stay; Mortality; Non-communicable chronic disease

Strengths and limitations of this study

- The first national study placing the CKD burden on hospital stay and mortality in the full context of all major NCDs.
- Large sample size and wide geographical coverage.
- Only tertiary hospitals were included, which might have led to population selection bias.
- Diagnosis of major NCDs was based on the ICD-10 coding with low sensitivity.
- Data of eGFR or proteinuria and information on medications were not available.

Background

There is a rising burden of non-communicable diseases (NCDs) at a global level. Two of three deaths each year are attributable to NCDs, and four-fifths of NCD-related deaths occur in low- and middle-income countries.[1] This exerts a significant influence on the healthcare system and costs worldwide.[2] Taking action against NCDs is, therefore, an economic imperative.[3] The priority actions for the NCD crisis were released by the United Nations High-Level Meeting in 2011, focusing on the prevention and control of heart disease, stroke, cancer, diabetes, and chronic respiratory diseases.[1] The world leaders also committed to reduce premature deaths from NCDs by one-third by 2030.[3]

Over the past decade, chronic kidney disease (CKD) has been recognized as a major public health issue worldwide, with an estimated prevalence of more than 10%.[4 5] By 2040, CKD is estimated to become the fifth leading cause of early death globally—one of the largest projected increases of any major cause of death.[6] In China, CKD is prevalent and is associated with more severe comorbidities and higher medical expenditures.[7 8] However, unlike other NCDs, such as diabetes, the awareness of CKD is low among patients and healthcare providers.[9] Besides, CKD is a key determinant of poor health outcomes of major NCDs and a risk multiplier in patients with cardiovascular disease (CVD), diabetes, and hypertension.[10] Due to the fact that the kidneys are usually target organs of systemic vascular, hemodynamic, metabolic, and inflammatory disorders, the pandemic of NCDs also leads to a persistently increasing morbidity of CKD.[11] There is accumulating evidence that major NCDs, including heart disease and stroke, have a poor prognosis in the presence of CKD.[12-14] Moreover, CKD has been reported to be associated with reduced implementation of best clinical practice, which could lead to suboptimal

treatment and adverse outcomes, especially for patients with CVD.[15]

Although CKD is a global health issue, to the best of our knowledge, there have been neither large-scale studies to quantitatively evaluate the burden of CKD on all major NCDs, nor studies comparing the burden of CKD with other NCDs. The evidence for the healthcare resource utilization associated with CKD and other major NCDs at a national level is limited, which impedes the development of effective preventive strategies. In addition, little is known about the status of cardiac procedures for patients with CKD in China. Hence, we initiated this observational study to comprehensively and quantitatively evaluate the healthcare resource utilization and prognosis of CKD and other NCDs, as well as to compare the burden of kidney diseases on the healthcare system with other NCDs among hospitalized patients in China.

Methods

Study population

The Hospital Quality Monitoring System (HQMS) is a mandatory patient-level national database for hospital accreditation under the authority of the National Health Commission of the People's Republic of China. Details of HQMS have been described elsewhere.[16 17] In brief, all tertiary hospitals in China have been requested to submit electronic inpatient discharge records to the HQMS on a daily basis. Unlike the Western medical system, tertiary hospitals in China provide primary, secondary, and tertiary care and have exposure to a nationwide patient population. Patient-level data were collected from uniform front pages of hospitalization medical records. Altogether 353 variables including demographic characteristics, clinical diagnoses, procedures, pathology

diagnoses, and expenditure breakdowns were collected. All personal information has already been de-identified to protect the patient privacy. The diagnoses were coded based on the International Classification of Diseases-10 (ICD-10) coding system by certified professional medical coders at every hospital. As the part of stringent standard practice in China, the inpatient discharge records have the legal validity and must be filed by the care-giving doctors who have the most accurate and comprehensive understanding of the patient's medical condition.

A total of 19,518,990 records of adult inpatients admitted from July 1, 2013 to June 30, 2014 in 29 provinces (excluding Hong Kong, Macao, Taiwan, Tibet, and Ningxia) were included in this cross-sectional study, with certain patients having more than one hospitalization. During this period, 715 tertiary hospitals in China, accounting for 44% of all tertiary hospitals in the country, had submitted inpatient records to the HQMS database. Hospitalizations were used in the present analysis since they are more relevant to the discussion of "disease burden".[18] This study was approved by the Ethics Committee of Peking University First Hospital (2015-928) and informed consent was waived by the Ethics Committee.

Definition of CKD

The ICD-10 coding of discharge diagnoses was used to identify patients with CKD.[16 17] Hospitalizations of patients with at least one of the following diagnoses (in both primary diagnosis and secondary diagnoses) were identified as having CKD (relevant ICD-10 coding in supplemental Appendix 1): glomerulonephritis, diabetic nephropathy, hypertensive nephropathy, obstructive nephropathy, renal cancer, tubulointerstitial

nephritis, kidney disease secondary to autoimmune diseases, kidney failure of unknown reason. Among patients' records with CKD, only 14% of them had the information on CKD staging.

Validation study

Since the laboratory results are not included in the HQMS dataset, we performed a validation study using 67,376 hospitalizations in three hospitals in the HQMS. Those were the pilot hospitals that accomplished the HQMS phase 2 data collection expansion to the data of laboratory tests and medications.[19] The estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease (MDRD) Study equation tailored for Chinese CKD patients.[20] Proteinuria was defined by urinary albumin-to-creatinine ratio (ACR) ≥30 mg/g creatinine, and/or urinary protein ≥trace in the urine routine test. CKD was defined as the presence of proteinuria and/or eGFR less than 60 ml/min/1.73 m^2. Compared with the gold standard, the sensitivity and specificity of CKD identification by ICD-10 coding was 34.2% and 97.8%, respectively.[19]

Definition of other NCDs

Major NCDs, including coronary heart disease (CHD), stroke, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), and cancer,[1] were identified by the ICD-10 coding of hospital discharge diagnoses (in both primary and secondary diagnoses, relevant ICD-10 coding in supplemental Appendix 1). Information on coronary angiography (CAG), percutaneous coronary intervention (PCI), and coronary artery

bypass grafting was obtained from the procedure coding of the inpatient discharge records for patients with CHD. For patients with multiple NCD diagnoses, each relevant diagnosis was identified and counted when stratified by the above NCDs.

Other covariates

Individual variables including age, sex, occupation (professional, worker, farmer, retired, unemployed, and others), type of health insurance (basic medical insurance, new rural cooperative medical care, other types of insurance, and uninsured), type of admission (emergency, routine, and others), and intensive care unit (ICU) stay were collected from the HQMS database.

Outcomes

Hospitalization costs and length of hospital stay, which are both important indicators for healthcare resource utilization, were acquired from the clinical charts in electronic inpatient discharge records. The total costs of the patient's hospitalization were jointly borne by the patient, the government, and related insurers, and included costs for prescribed drugs, hospital beds, laboratory tests, medical examinations, and surgical costs. The total cost information was summarized and reported by each hospital, and we extracted it directly from the HQMS database. Information on in-hospital mortality was also collected to assess the prognosis of patients. The survival status of each patient was verified based on the discharge status and combined with the information of autopsy.

Statistical analysis

General characteristics stratified by the presence of CKD for each NCD were described. Continuous data were presented as mean ± standard deviation, or as median (interquartile range) for highly skewed variables. Categorical variables were presented as proportions. All of the analyses were based on the hospitalizations (patient records), not individuals.

The effects of CKD on the healthcare resource utilization for each NCD were analyzed using generalized regression models for log-transformed cost and length of stay with log-link function and gamma distribution. Due to the low mortality and large sample size, Poisson regression model was used to evaluate the burden of CKD and other NCDs on in-hospital mortality. Percent of change (% change) and relative risk (RR) with 95% confidence interval (CI) were calculated as exp(β)–1 from the generalized regression model and exp(β) from the Poisson regression model, respectively. For the purpose of assessing additional effects of CKD, covariates included in the model for the sub-dataset of each NCD were age (5-year categories, except for 18–25 years and >80 years), sex (male vs. female), type of health insurance (dummy variable), type of admission (dummy variable), ICU stay (yes vs. no), presence of CKD (yes vs. no), presence of other NCDs (yes vs. no), pneumonia (yes vs. no), and sepsis (yes vs. no).

Then, the presence of CKD and other NCDs was included in the models simultaneously, using the data of all hospitalized patients, in order to compare the effect of CKD with that of other NCDs on outcome variables. Similar covariates were used as described previously.

For hospitalized patients with CHD, the percentages of those with CAG and PCI were reported among different clinical types (including ST-segment elevation myocardial infarction, non-ST-segment elevation myocardial infarction, and non-acute coronary

syndrome), stratified by the presence of CKD. Among 18,315 hospitalizations with CHD and with available CKD staging, the percentages of those with CAG and PCI were also reported.

The sensitivity analysis was conducted among patients with CKD stages 3-5 to further determine the healthcare resource utilization of CKD (Appendices 2 and 3). All analyses were performed using the SAS software, version 9.4 (SAS Institute Inc, Cary, NC). Due to the large sample size of our study, *P* values were not reported for between-group comparisons.

Patient and public involvement statement

Patients or the public were not involved in this study.

Results

Among 19.5 million hospitalizations, the percentages of diagnosed CKD, CHD, stroke, hypertension, diabetes, COPD, and cancer were 4.5%, 9.2%, 8.2%, 18.8%, 7.9%, 2.3%, and 19.4%, respectively (table 1). For each major NCD, individuals with CKD were older (except for hypertension); were more often male and urban residents; more often stayed in ICU and had infectious diseases such as pneumonia and sepsis (except for COPD).

For each major NCD, the presence of CKD was independently associated with longer hospital stay, with increased percentages ranging from 7.69% (95% CI, 7.11%–8.28%, for stroke) to 21.60% (95% CI, 21.09%–22.10%, for CHD) (Table 2). After adjusting for potential confounders, the presence of CKD was associated with higher costs for stroke (11.15%; 95% CI, 10.31%–11.99%), COPD (19.46%; 95% CI, 17.97%–

20.97%), and cancer (18.88%; 95% CI, 17.98%–19.78%). In contrast, the costs were slightly lower for CHD (acute coronary syndrome or non-acute coronary syndrome) (−1.08%; 95% CI, −1.71% to −0.45%), hypertension (−0.22%; 95% CI, −0.60% to 0.16%), and diabetes (−0.97%; 95% CI, −1.43% to –0.51%) in the presence of CKD (Table 2). If patients with CHD were excluded, the presence of CKD was associated with increased costs for patients with hypertension and diabetes, with a fully adjusted change of 2.70% (95% CI, 2.24%–3.15%) and 4.11% (95% CI, 3.56%–4.66%), respectively. The in-hospital mortality was also higher in the presence of CKD for major NCDs, with fully adjusted RR ranging from 1.91 (95% CI, 1.82–1.99, for stroke; 95% CI, 1.85–1.97, for hypertension) to 2.65 (95% CI, 2.55–2.75, for cancer) (Table 2).

Among hospitalizations with CHD, the percentages of individuals with CAG and PCI were substantially lower for those with CKD (Figure 1). A similar pattern was observed for coronary artery bypass grafting, which was 0.3% and 1.0% for CHD patients with or without CKD, respectively. Even for those with acute coronary syndrome or cardiogenic shock—a strong indication for emergency PCI[21]—the trend was still similar: 11.9% vs. 22.2% for ST-elevated myocardial infarction, and 3.5% vs. 7.3% for non-ST elevated myocardial infarction. Furthermore, among hospitalizations with available CKD staging and with CHD, the percentages of individuals with CAG and PCI were lower even for stage 1 and 2, compared with those without CKD and with CHD (Figure 1).

Compared with other NCDs, CKD had the highest increase in length of hospital stay (22.09%; 95% CI, 21.87%–22.32%) (Table 3). Cancer and CHD were associated with the highest contribution to increased costs for hospitalized patients, which was 39.47% (95%

CI, 39.29%–39.65%) and 30.95% (95% CI, 30.71%–31.19%), respectively. CKD was associated with 6.82% (95% CI, 6.56%–7.08%) increased costs. Furthermore, CKD resulted in the second highest in-hospital mortality (RR, 2.23; 95% CI, 2.19–2.28), which was only lower than that of cancer (RR, 2.87; 95% CI, 2.83–2.91).

Discussion

This study is the first national quantitative study on the burden of CKD and other major NCDs on the healthcare system in China. The findings of this study indicated that the presence of CKD was associated with additional burden on the healthcare system and increased in-hospital mortality for each major NCD, despite evidence of under-utilization of cardiac procedures in the presence of CKD. Furthermore, the healthcare resource utilization of CKD was comparable to those of other major NCDs in this large national sample of 19.5 million hospitalizations.

Studies regarding the utilization of healthcare resources for CKD mostly focused on end-stage kidney disease (ESKD).[22-24] The US Renal Data System 2019 Annual Data Report showed that the costs for both CKD and ESKD were in excess of $120 billion in 2017, and the latter accounted for more than 7.2% of the total Medicare expenditure.[25] Our study revealed that CKD was associated with a 6.8% increase in costs, which was higher than that of hypertension, diabetes, and COPD. Moreover, for each major NCD, the presence of CKD led to longer hospital stay, which is also an important marker for the healthcare resource utilization. Furthermore, considering the evidence of therapeutic nihilism for patients with CKD (documented for cardiac revascularization) and the insensitivity of diagnostic codes for CKD, the burden of CKD on the healthcare system

might be underestimated. A recent systematic review has also shown that the risks of adverse cardiovascular outcomes increase with CKD and are associated with substantial additional costs and resource utilization.[26]

Several previous studies have reported that both the general and high-risk populations have poor prognoses in the presence of kidney diseases. For example, using the data of 1.1 million adults within a large integrated healthcare system, Go *et al*. observed increased risks of all-cause mortality, CVD, and hospitalization associated with reduced kidney function.[12] A recent meta-analysis has reported that both reduced eGFR and elevated urinary albumin-to-creatinine ratio are associated with increased all-cause and cardiovascular mortality in the general population.[27] Similarly, using data from over 40 cohorts involving one million participants, it has been reported that the adjusted hazard ratio for all-cause mortality at an eGFR of 45 ml/min/1.73 m^2 was 1.24 (95% CI, 1.11–1.39) for those with hypertension,[28] and was 1.35 (95% CI 1.18–1.55) for those with diabetes,[29] compared with those with eGFR of 95 ml/min/1.73 m^2. In this study, we further expanded the observation to a range of other major NCDs, including CHD, stroke, COPD, and cancer. We found that CKD was consistently associated with the increased in-hospital mortality for each major NCD, and its impact was higher compared with that of the majority of NCDs, even comparable to that of cancer. These findings further highlight the importance of CKD as a major health burden and are consistent with the implications of Global Burden of Disease, Injuries, and Risk Factors Study, which has shown the high burden and rapid growth of CKD as a direct cause of morbidity and mortality.[4 6]

The potential mechanisms for the association of CKD and adverse outcomes are

complex and not fully understood. A previous study indicated that impaired kidney function could lead to multiple adverse systemic alterations, including inappropriate activation of the renin-angiotensin system, catalytic iron-dependent oxidative stress, endothelial dysfunction, and inflammation.[14] In addition, for patients whose CKD is a result of a systemic disease such as diabetes, kidney diseases might only serve as a marker of the severity of the target organ damage.

Another explanation for the adverse outcomes observed in patients with CKD might be that the presence of CKD is associated with the reduced implementation of best practice. Although the accumulating evidence and the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines with international consensus suggest that the level of care for ischemic heart disease offered to patients with CKD should not be prejudiced by their CKD,[30] our data on revascularization indicate that the cardiac treatment for patients with CKD is suboptimal. Under-utilization of aspirin, beta-blockers, angiotensin-converting enzyme inhibitors, glycoprotein IIb/IIIa receptor antagonists, and thrombolytic therapy has been observed in CKD patients due to concerns of bleeding risk, worsening of kidney function, and comorbidities.[15] A recent study from the United States indicated that, compared with those without CKD, patients with CKD reported more medication use for cardiovascular risk factors but had poorer risk factor control.[31] In our study, the percentages of hospitalizations with CAG and PCI were much lower for those with CKD, even for those with relatively well-preserved kidney function, consistent with the practice outside of China.[15] A recent meta-analysis has revealed that for patients with pre-dialysis CKD and with unstable angina or non-ST-segment-elevation myocardial infarction, an early invasive strategy is associated with the risk of re-hospitalization and reduced risk of

death and non-fatal re-infarction.[32] However, the risk of adverse clinical events after coronary revascularization and the percentage of later additional PCI are also increased in patients with CKD.[33 34] Hence, a multidisciplinary team involving various subspecialties is needed to improve the quality of care for CKD patients, and appropriate management by primary care clinicians is necessary to prevent CKD-associated adverse outcomes.[35]

To our knowledge, this is the first study that places the CKD burden on hospital stay and mortality in the full context of all major NCDs in a national database with large sample size and wide geographical coverage, which enables us to analyze the burden of multiple major NCDs simultaneously. However, our study does have some limitations. First, although our data were restricted to hospitalized patients, hospitalization inherently reflects the indication for admission and referral as well as disease burden. Only tertiary hospitals were included in our analyses, which might have led to population selection bias; nevertheless, 715 hospitals in our study covered almost all provinces of China and included all types of tertiary hospitals. Second, the diagnosis of CKD and major NCDs in hospitalized patients was based on the ICD-10 coding, which has the low sensitivity. Severe cases of CKD were likely to be diagnosed, which might affect the extrapolation of the results and lead to a potential overestimation of the excess risk associated with CKD. However, the high specificity of CKD identification (97.8%) is the strength of our study. Third, the low usage of CKD-staging codes was a limitation that should be recognized. Further evaluation of the healthcare utilization in different CKD stages is worthwhile. Fourth, since hospitalizations were identified using both primary and secondary diagnoses, the direct contribution of specific NCDs to health resource utilization might have been compromised. All of the analyses were based on the hospitalizations, and cases

reported in the results were not mutually exclusive, which may also affect the estimations of the true burden of disease. Finally, data on eGFR or proteinuria and information on medications used and the severity of major NCDs were not available for all patient records in our dataset.

Conclusions

In a systematic national assessment of diagnosed NCDs over 19.5 million hospitalizations in China, we showed that the adverse effects of CKD at both individual level and healthcare system level were comparable to those of other major NCDs, and the presence of CKD was associated with poor prognosis of other NCDs. Therefore, CKD should be integrated into the global prevention strategy of NCDs. In consideration of the complexity of the disease, a multilevel interdisciplinary approach will be needed to address the public health burden of CKD.

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Contributors

HW and LZ conceived and coordinated the study and acquired the data. CY, HW, and LZ designed the study. CY and LZ searched the literature. CY and JL prepared the figure. CY, HW, and LZ wrote the first draft manuscript. CY, JL, SY, and ZZ contributed to the analysis. CY, JL, SY, ZZ, JW, M-HZ, HW, LZ, and JC contributed to the interpretation.

CY, JL, SY, ZZ, JW, M-HZ, HW, LZ, and JC edited the manuscript. All authors critically reviewed the manuscript and approved the final version.

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Competing interests

JC was partly supported by grants to the CKD Prognosis Consortium by the National Kidney Foundation and NIH.

Patient and public involvement statement

Patients or the public were not involved in this study.

Patient consent for publication

Not required.

Ethics approval

Ethical approval was obtained from the Ethics Committee of Peking University First Hospital (2015-928).

Data availability statement

The data that support the findings of this study are available from the Bureau of Medical Administration and Medical Service Supervision, National Health Commission of China but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the Bureau of Medical Administration and Medical Service Supervision, National Health Commission of China.

Supplementary material

Appendix 1. The International Classification of Diseases-10 coding of chronic kidney disease and other major non-communicable chronic diseases

Appendix 2. Effects of chronic kidney disease stages 3-5 on length of stay, costs, and in-hospital mortality for each non-communicable disease

Appendix 3. Effects of chronic kidney disease stages 3-5 on length of stay, costs, and in-hospital mortality, compared with other major non-communicable diseases

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Figure 1. Percentages of hospitalizations with coronary angiography and percutaneous coronary intervention for individuals with coronary heart disease

Note: The number of hospitalizations with or without CKD was 3,116 and 68,616 for STEMI, respectively; 2,645 and 25,057 for NSTEMI, respectively; and 124,388 and 1,519,864 for NACS, respectively. For 18,315 hospitalizations with available CKD staging, 15.8%, 24.6%, 16.8%, and 42.9% of individuals were in stages 1–2, 3, 4, and 5, respectively.

Abbreviations: CKD, chronic kidney disease; NACS, non-acute coronary syndrome; NSTEMI, non-ST-segment-elevation myocardial infarction; STEMI, ST-segment-elevation myocardial infarction.

Table 1. Characteristics of hospitalized patients with non-communicable chronic diseases stratified by the presence of chronic kidney disease

	CHD		Stroke		Hypertension		Diabetes		COPD		Cancer		Total	
	CKD	Non-CKD	CKD	Non-CKD	CKD	Non-CKD	CKD	Non-CKD	CKD	Non-CKD	CKD	Non-CKD	CKD	Non-CKD
Number	132032	1665601	79 906	1529843	348075	3322665	222157	1321816	22998	429475	22585	3698423	871742	18647248
Percentage (%)	0.7	8.5	0.4	7.8	1.8	17.0	1.1	6.8	0.1	2.2	0.4	19.0	4.5	95.5
Main outcomes														
Costs (1000 yuan)	11 (7-20)	9 (6-20)	11 (7-19)	9 (6-16)	10 (6-17)	9 (6-16)	10 (7-16)	9 (6-16)	12 (8-22)	10 (6-16)	17 (7-29)	10 (6-20)	9 (6-17)	8 (4-14)
Length of stay (days) †	11 (8-17)	9 (6-13)	12 (8-17)	11 (7-15)	11 (7-16)	9 (6-14)	12 (8-16)	10 (7-14)	12 (8-19)	10 (7-15)	11 (7-19)	8 (4-14)	11 (6-16)	8 (5-13)
Mortality (%)	3.5	1.4	3.5	1.5	1.8	0.9	1.8	0.9	4.9	1.9	5.0	1.0	1.8	0.6
Demographic characteristics														
Age (years)	71.4±11.8	68.1±12.0	69.1±13.0	65.9±12.9	64.7±14.3	65.7±12.3	63.7±13.2	63.3±12.8	76.7±9.6	72.8±10.3	62.1±13.8	56.7±13.3	57.7±17.0	52.7±17.6
Male (%)	60.2	55.4	62.6	55.1	59.4	52.2	57.6	53.1	76.6	71.7	63.4	49.7	57.3	45.6
Occupation (%)†														
Professional	7.6	8.7	8.0	8.5	9.8	9.2	11.0	11.2	4.2	4.2	10.4	11.1	11.9	14.4
Worker	4.9	5.3	5.6	5.9	5.9	5.9	6.5	6.3	3.8	4.7	6.2	6.2	6.6	7.1
Farmer	11.8	18.1	15.7	23.0	15.6	19.1	14.7	15.8	15.2	23.2	17.6	24.7	21.3	21.5
Retired	40.9	32.4	36.6	27.7	30.6	28.7	31.0	28.3	42.3	31.3	25.3	14.5	20.7	13.8
Unemployed	7.0	6.3	7.1	7.4	8.6	7.3	8.7	7.4	7.5	7.8	8.6	9.7	9.4	10.1
Others	27.8	29.4	27.0	27.4	29.5	29.9	28.2	31.1	27.1	28.9	31.9	33.7	30.2	33.1
Health insurance (%)														
Basic medical insurance	66.0	59.0	62.7	54.0	59.6	57.0	62.3	59.9	63.1	54.3	71.2	43.0	49.9	42.9
NRCMC	12.5	18.7	15.8	22.6	16.9	19.4	15.8	16.7	15.5	24.4	9.8	26.7	23.2	22.5
Others	11.0	11.6	9.8	10.3	10.6	10.3	9.9	10.3	10.2	10.0	13.6	12.7	11.4	13.0
Uninsured	10.5	10.8	11.8	13.1	12.9	13.3	12.0	13.1	11.2	11.3	5.5	17.6	15.4	21.6
Admission and comorbidity information														
Admission (%)†														
Emergency	21.6	22.6	25.3	29.3	17.3	20.5	16.5	16.9	22.9	23.1	10.8	7.4	16.1	17.9
Routine	71.6	69.4	68.3	63.2	76.0	72.2	76.6	75.1	69.1	68.9	80.1	82.4	76.0	72.6
Others	6.8	7.9	6.5	7.6	6.7	7.4	6.9	8.0	8.0	8.0	9.2	10.2	7.9	9.5
ICU stay (%)	4.1	3.0	3.9	2.7	2.4	2.0	2.2	1.7	5.1	3.2	2.0	0.7	2.0	1.2
Hypertension (%)	69.6	55.3	71.1	56.6	--	--	62.7	52.6	54.8	33.6	32.3	12.2	39.9	17.8
CHD (%)	--	--	28.2	18.7	26.4	27.7	26.8	25.8	35.9	23.0	9.4	2.9	15.2	8.9
Stroke (%)	17.1	17.1	--	--	16.3	26.0	14.8	18.9	12.7	9.5	4.8	1.8	9.2	8.2
COPD (%)	6.2	5.9	3.7	2.7	3.6	4.3	2.6	3.1	--	--	2.2	1.1	2.6	2.3
Cancer (%)	5.7	6.5	4.9	4.4	7.5	13.5	5.0	13.4	7.9	9.6	--	--	9.2	19.8

Diabetes (%)	45.0	20.5	41.2	16.3	40.0	20.9	--	--	24.6	9.6	33.7	4.8	25.5	7.1
Pneumonia (%)	6.1	4.1	5.8	3.6	4.3	3.6	4.3	3.4	8.3	8.5	7.7	2.0	3.7	2.3
Sepsis (%)	0.5	0.2	0.7	0.2	0.5	0.2	0.7	0.3	0.7	0.3	0.6	0.2	0.6	0.2

[†]The percentages of missing values for occupation, type of admission, and length of stay were 10.9%, 6.4%, and 16.6% for CHD; 10.5%, 7.1%, and 17.5% for stroke; 10.7%, 6.7%, and 16.2% for hypertension; 10.7%, 6.9%, and 16.6% for diabetes; 12.2%, 5.4%, and 18.0% for COPD; and 11.4%, 6.1%, and 15.2% for cancer.

Abbreviations: CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; NCDs, non-communicable chronic diseases; NRCMC, New Rural Cooperative Medical Care.

Table 2. Effects of chronic kidney disease on length of stay, costs, and in-hospital mortality for each non-communicable disease

Condition	Covariates in the model	Length of stay % change (95% CI)	Costs % change (95% CI)	In-hospital mortality relative risk (95% CI)
CHD	Model 1	24.58 (24.1, 25.06)	4.96 (4.34, 5.58)	2.15 (2.08, 2.22)
	Model 2	21.99 (21.49, 22.5)	−0.26 (−0.90, 0.37)	2.09 (2.02, 2.16)
	Model 3	21.60 (21.09, 22.10)	−1.08 (−1.71, −0.45)	2.02 (1.95, 2.09)
Stroke	Model 1	11.35 (10.80, 11.90)	16.65 (15.81, 17.49)	2.17 (2.08, 2.26)
	Model 2	8.26 (7.68, 8.85)	13.05 (12.19, 13.91)	2.01 (1.92, 2.10)
	Model 3	7.69 (7.11, 8.28)	11.15 (10.31, 11.99)	1.91 (1.82, 1.99)
Hypertension	Model 1	14.46 (14.17, 14.74)	−0.40 (−0.76, −0.04)	1.94 (1.89, 2.00)
	Model 2	16.24 (15.92, 16.55)	0.49 (0.10, 0.87)	1.97 (1.91, 2.03)
	Model 3	16.01 (15.70, 16.33)	−0.22 (−0.60, 0.16)	1.91 (1.85, 1.97)
Diabetes	Model 1	14.05 (13.70, 14.41)	−2.90 (−3.33, −2.47)	1.88 (1.82, 1.95)
	Model 2	16.55 (16.16, 16.94)	−0.14 (−0.60, 0.33)	2.02 (1.94, 2.10)
	Model 3	16.32 (15.93, 16.70)	−0.97 (−1.43, −0.51)	1.95 (1.88, 2.03)
COPD	Model 1	15.85 (14.84, 16.87)	31.41 (29.78, 33.06)	2.21 (2.08, 2.35)
	Model 2	11.14 (10.11, 12.18)	20.15 (18.65, 21.68)	1.99 (1.86, 2.13)
	Model 3	11.05 (10.02, 12.09)	19.46 (17.97, 20.97)	1.97 (1.84, 2.11)
Cancer	Model 1	21.38 (20.66, 22.11)	25.84 (24.96, 26.72)	3.30 (3.19, 3.41)
	Model 2	17.87 (17.11, 18.64)	19.63 (18.72, 20.54)	2.75 (2.65, 2.85)
	Model 3	17.50 (16.74, 18.26)	18.88 (17.98, 19.78)	2.65 (2.55, 2.75)

Note: Numbers in the table are percent-changes/relative risks of patient records with CKD compared with patient records without CKD for each non-communicable disease. Percent of change (% change) and relative risk with 95% confidence interval (CI) were calculated as exp(β)–1 from the generalized regression model and exp(β) from the Poisson regression model, respectively.

Covariates in model 1 included age and sex.

Covariates in model 2 included age, sex, occupation, type of health insurance, type of admission, intensive care unit stay, presence of CHD, stroke, hypertension, diabetes, COPD, and cancer (except for the disease used to define the subgroup).

Covariates in model 3 included covariates in model 2, plus the presence of sepsis and pneumonia.

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

Table 3. Effects of chronic kidney disease on length of stay, costs, and in-hospital mortality, compared with other major non-communicable diseases

Condition	Covariates in the model	Length of stay % change (95% CI)	Costs % change (95% CI)	In-hospital mortality relative risk (95% CI)
CKD	Model 1	22.34 (22.14, 22.55)	6.49 (6.25, 6.73)	2.31 (2.27, 2.35)
	Model 2	22.09 (21.87, 22.32)	6.82 (6.56, 7.08)	2.23 (2.19, 2.28)
CHD	Model 1	−5.19 (−5.31, −5.07)	27.72 (27.51, 27.94)	1.36 (1.34, 1.38)
	Model 2	−7.31 (−7.44, −7.18)	30.95 (30.71, 31.19)	1.31 (1.29, 1.33)
Stroke	Model 1	16.12 (15.97, 16.27)	9.29 (9.10, 9.48)	1.58 (1.56, 1.60)
	Model 2	17.34 (17.17, 17.51)	9.90 (9.69, 10.11)	1.70 (1.67, 1.73)
Hypertension	Model 1	5.49 (5.39, 5.59)	8.90 (8.77, 9.04)	0.93 (0.92, 0.94)
	Model 2	1.81 (1.69, 1.92)	4.85 (4.70, 5.01)	0.76 (0.75, 0.77)
Diabetes	Model 1	11.36 (11.22, 11.51)	5.05 (4.87, 5.23)	1.13 (1.11, 1.15)
	Model 2	8.96 (8.80, 9.12)	1.00 (0.81, 1.20)	0.99 (0.97, 1.01)
COPD	Model 1	3.89 (3.65, 4.14)	−9.00 (−9.29, −8.71)	1.31 (1.28, 1.34)
	Model 2	5.77 (5.50, 6.04)	−8.67 (−8.98, −8.36)	1.24 (1.21, 1.27)
Cancer	Model 1	8.90 (8.80, 9.00)	27.40 (27.25, 27.55)	2.00 (1.97, 2.02)
	Model 2	13.90 (13.79, 14.02)	39.47 (39.29, 39.65)	2.87 (2.83, 2.91)

Note: Numbers in the table are percent-changes/relative risks of patient records with corresponding disease compared with patient records without corresponding disease. Percent of change (% change) and relative risk with 95% confidence interval (CI) were calculated as exp(β)–1 from the generalized regression model and exp(β) from the Poisson regression model, respectively.

Covariates in model 1 included age and sex.

Covariates in model 2 included age, sex, occupation, type of health insurance, type of admission, intensive care unit stay, presence of CKD, CHD, stroke, hypertension, diabetes, COPD, and cancer, and presence of sepsis and pneumonia.

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

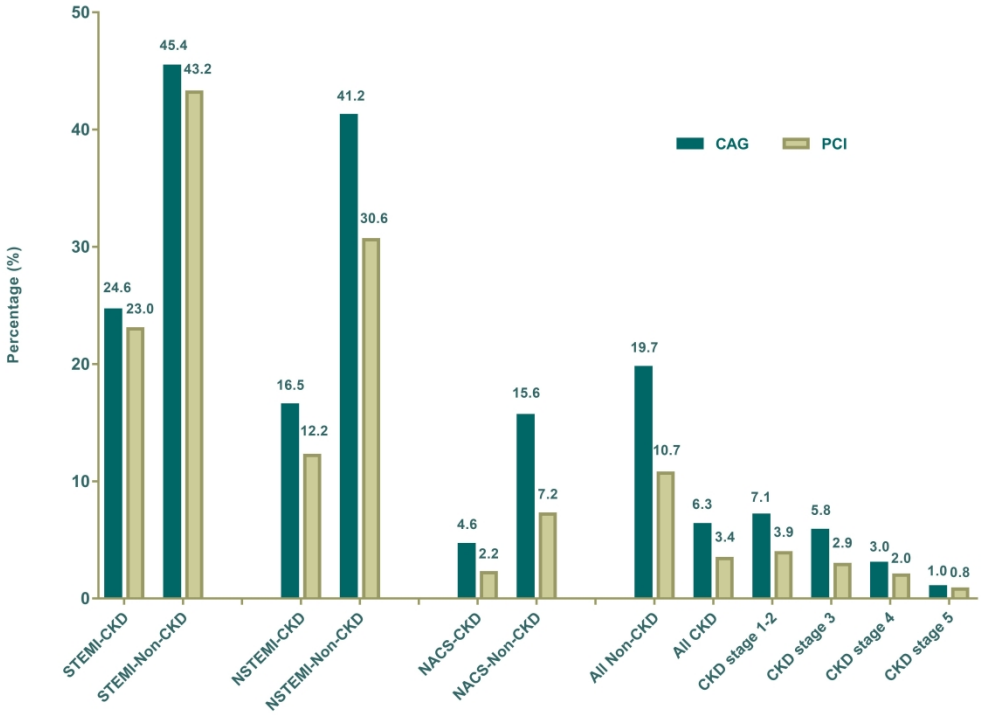

Figure 1. Percentages of coronary angiography and percutaneous coronary intervention for hospitalizations with coronary heart disease

Note: The number of hospitalizations with or without CKD was 3,116 and 68,616 for STEMI, 2,645 and 25,057 for NSTEMI, 124,388 and 1,519,864 for NACS, respectively. For 18,315 hospitalizations with diagnoses of CKD staging, 15.8%, 24.6%, 16.8%, and 42.9% of them were in stage 1-2, 3, 4 and 5.

Abbreviations: CKD, chronic kidney disease; NACS, non-acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction.

227x170mm (600 x 600 DPI)

Appendix 1. The International Classification of Diseases-10 coding of chronic kidney disease and other major non-communicable chronic diseases

Disease		ICD-10 coding
CKD		E10.2+, E11.2+, E13.2+, E14.2+, I12.0, I12.9, I13.0, I13.1, I13.2, I13.9, N11, N12, N14, N15, N16.*, E74.8, E72.0, N25.1, M32.1+N08.5*, M32.1+N16.4*, M35.0+N16.4*, M31.0+N08.5*, M31.7+N08.5*, M31.001‡, M31.802‡, M32.101+N08.5*†, M31.102+N08.5*†, M31.303+N08.5*†, N18, N19, N13.0, N13.1, N13.2, C64, N07, N08 (excluding N08.5*), N13.6, Q60, Q61.1, Q61.2, Q61.3, Q61.5, Q63.1, Q63.9, M10.3, N26, N28.0, N28.8, N28.9, A52.7+N08.0*, N99.0, P96.0, R39.2, K76.7, Q27.1, I70.1, M31.4 (combined with I15.0) N00.8, N02, N03, N04, N05, N06, N39.1
CHD	CHD†	I21.001, I21.002, I21.004, I21.101, I21.103, I21.104, I21.105, I21.201, I21.202, I21.203, I21.204, I21.205, I21.206, I21.207, I21.208, I21.209, I21.210, I21.211, I21.213, I21.214, I21.215, I21.301, I21.302, I21.304, I21.907, I21.403, I24.003, I20.001, I20.002, I20.003, I20.004, I20.005, I20.006, I20.101, I20.102, I20.802, I20.803, I21.303, I21.401, I21.402, I21.901, I21.902, I21.910, I22.001, I22.101, I22.801, I22.802, I22.803, I22.901, I23.001, I23.002, I23.101, I23.201, I23.301, I24.001, I24.002, I24.003, I24.004, I24.005, I24.006, I24.101, I24.102, I24.801, I24.802, I24.901, I20.801, I20.804, I20.805, I20.806, I20.902, I25.103, I25.104, I25.105, I25.201, I25.202, I25.203, I25.204, I25.205, I25.206, I25.207, I25.208, I25.209, I25.210, I25.211, I25.212, I25.213, I25.214, I25.215, I25.501, I25.601, I25.901, I25.902
	CHD‡	I21.000, I21.001, I21.002, I21.003, I21.004, I21.005, I21.006, I21.007, I21.100, I21.101, I21.102, I21.103, I21.104, I21.105, I21.200, I21.201, I21.202, I21.203, I21.204, I21.205, I21.206, I21.300, I21.301, I21.401, I20.000, I20.001, I20.002, I20.003, I20.004, I20.005, I20.006, I20.100, I20.101, I20.102, I20.804, I21.302, I21.303, I21.400, I21.402, I21.900, I22.000, I22.100, I22.800, I22.900, I23.000, I23.100, I23.200, I23.300, I23.400, I23.500, I23.600, I23.601, I23.800, I24.000, I24.001, I24.100, I24.101, I24.800, I24.801, I24.900, I24.901, I20.801, I20.802, I20.803, I20.804, I20.900, I25.000, I25.100, I25.101, I25.102, I25.103, I25.200, I25.500, I25.600, I25.800, I25.801, I25.900, I25.901,
COPD		J44.901†, J44.003†, J44.103†, J44.900‡, J44.000‡, J44.100‡, J44.800‡
Stroke		I60, I61, I63, I64, G45, H34.1
Diabetes		E10, E11, E12, E13, E14
Cancer		C00-C26, C30-C34, C37-C41, C43-C58, C60-C85, C88, C90-C97, D00-D07, D09, D37-D48, B21, Z85, Z08 Z51.10†, Z51.20†, Z51.50†, Z03.101†, E87.805†, O99.8011†, O99.8021†, O99.8024†, O99.8031†, Z51.00‡, Z51.10‡, Z51.80‡, Z03.10‡, O99.802‡, Z35.802‡, Z54.001‡, E88.805‡, Z86.000‡
Hypertension		I10

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Disease	ICD-10 coding
Sepsis	A41
Pneumonia	J12-J18

†Applicable for ICD-10 (Beijing Version 4.0) only.

‡Applicable for ICD-10 (National Standard Version1.0) only.

*Denotes to any possible number so that the whole sequence represents all the subclasses of the disease.

Abbreviations: CHD, coronary heart disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary diseases. ICD-10, International Classification of Diseases-10.

Appendix 2. Effects of chronic kidney disease stages 3-5 on length of stay, costs, and in-hospital mortality for each non-communicable disease

Condition	Covariates in the model	Length of stay % change (95% CI)	Costs % change (95% CI)	In-hospital mortality relative risk (95% CI)
CHD	Model 1	36.67 (35.19, 38.17)	14.54 (12.64, 16.47)	1.90 (1.73, 2.08)
	Model 2	38.68 (37.07, 40.30)	6.22 (4.35, 8.13)	1.93 (1.76, 2.13)
	Model 3	38.41 (36.81, 40.03)	5.69 (3.83, 7.58)	1.93 (1.76, 2.13)
Stroke	Model 1	22.81 (20.89, 24.75)	30.39 (27.46, 33.38)	2.12 (1.88, 2.39)
	Model 2	21.76 (19.67, 23.88)	25.48 (22.49, 28.55)	1.92 (1.69, 2.19)
	Model 3	21.13 (19.05, 23.24)	23.60 (20.66, 26.60)	1.79 (1.58, 2.05)
Hypertension	Model 1	19.77 (19.01, 20.54)	0.62 (-0.29, 1.53)	1.60 (1.49, 1.72)
	Model 2	25.88 (25.02, 26.75)	4.10 (3.10, 5.11)	1.83 (1.69, 1.98)
	Model 3	25.69 (24.83, 26.55)	3.47 (2.48, 4.47)	1.76 (1.63, 1.91)
Diabetes	Model 1	23.75 (22.71, 24.80)	10.24 (8.92, 11.58)	1.91 (1.75, 2.09)
	Model 2	29.22 (28.06, 30.40)	13.22 (11.80, 14.65)	2.14 (1.95, 2.36)
	Model 3	29.06 (27.90, 30.23)	12.55 (11.15, 13.98)	2.13 (1.93, 2.34)
COPD	Model 1	14.97 (11.79, 18.25)	36.41 (31.07, 41.97)	1.70 (1.37, 2.12)
	Model 2	15.21 (11.75, 18.77)	22.93 (17.93, 28.14)	1.74 (1.38, 2.19)
	Model 3	15.38 (11.92, 18.95)	22.80 (17.83, 27.97)	1.72 (1.36, 2.16)
Cancer	Model 1	24.54 (21.36, 27.80)	20.65 (17.08, 24.34)	2.15 (1.86, 2.49)
	Model 2	20.58 (17.23, 24.02)	12.13 (8.53, 15.85)	1.68 (1.44, 1.95)
	Model 3	19.72 (16.40, 23.14)	11.26 (7.70, 14.94)	1.49 (1.28, 1.73)

Note: Numbers in the table are percent-changes/relative risks of patient records with CKD compared with patient records without CKD

for each non-communicable disease. Percent of change (% change) and relative risk with 95% confidence interval (CI) were calculated as exp(β)–1 from the generalized regression model and exp(β) from the Poisson regression model, respectively.

Covariates in model 1 included age and sex.

Covariates in model 2 included age, sex, occupation, type of health insurance, type of admission, intensive care unit stay, presence of CHD, stroke, hypertension, diabetes, COPD, and cancer (except for the disease used to define the subgroup).

Covariates in model 3 included covariates in model 2, plus the presence of sepsis and pneumonia.

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

Appendix 3. Effects of chronic kidney disease stages 3-5 on length of stay, costs, and in-hospital mortality, compared with other major non-communicable diseases

Condition	Covariates in the model	Length of stay % change (95% CI)	Costs % change (95% CI)	In-hospital mortality relative risk (95% CI)
CKD	Model 1	32.02 (31.40, 32.65)	14.97 (14.26, 15.70)	1.76 (1.67, 1.85)
	Model 2	35.61 (34.93, 36.30)	19.65 (18.86, 20.45)	1.92 (1.82, 2.02)
CHD	Model 1	-5.95 (-6.08, -5.83)	28.00 (27.78, 28.22)	1.34 (1.32, 1.36)
	Model 2	-7.67 (-7.80, -7.53)	31.31 (31.06, 31.56)	1.32 (1.29, 1.34)
Stroke	Model 1	16.71 (16.55, 16.86)	9.00 (8.81, 9.20)	1.62 (1.60, 1.65)
	Model 2	17.76 (17.59, 17.94)	9.58 (9.37, 9.80)	1.74 (1.71, 1.77)
Hypertension	Model 1	5.07 (4.97, 5.18)	9.26 (9.11, 9.40)	0.92 (0.91, 0.93)
	Model 2	2.15 (2.03, 2.26)	5.11 (4.95, 5.27)	0.78 (0.76, 0.79)
Diabetes	Model 1	10.38 (10.23, 10.53)	5.90 (5.70, 6.10)	1.09 (1.07, 1.11)
	Model 2	9.54 (9.37, 9.71)	1.90 (1.69, 2.11)	1.03 (1.01, 1.05)
COPD	Model 1	3.99 (3.74, 4.24)	-9.96 (-10.25, -9.67)	1.32 (1.29, 1.35)
	Model 2	5.83 (5.56, 6.11)	-9.48 (-9.80, -9.17)	1.24 (1.21, 1.27)
Cancer	Model 1	9.51 (9.41, 9.60)	26.96 (26.80, 27.11)	2.00 (1.98, 2.03)
	Model 2	14.07 (13.95, 14.18)	38.95 (38.76, 39.13)	2.87 (2.82, 2.91)

Note: Numbers in the table are percent-changes/relative risks of patient records with corresponding disease compared with patient records without

corresponding disease. Percent of change (% change) and relative risk with 95% confidence interval (CI) were calculated as exp(β)–1 from the generalized regression model and exp(β) from the Poisson regression model, respectively.

Covariates in model 1 included age and sex.

Covariates in model 2 included age, sex, occupation, type of health insurance, type of admission, intensive care unit stay, presence of CKD, CHD, stroke, hypertension, diabetes, COPD, and cancer, and presence of sepsis and pneumonia.

Abbreviations: CHD, coronary heart disease; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease.

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3-4
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	6-7
Objectives	3	State specific objectives, including any prespecified hypotheses	7
Methods			
Study design	4	Present key elements of study design early in the paper	8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7-8
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	8
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	8-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	8-10
Bias	9	Describe any efforts to address potential sources of bias	9-10
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	10
		(*b*) Describe any methods used to examine subgroups and interactions	10
		(*c*) Explain how missing data were addressed	-
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	10
		(*e*) Describe any sensitivity analyses	-
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	11
		(b) Give reasons for non-participation at each stage	-
		(c) Consider use of a flow diagram	-
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	11
		(b) Indicate number of participants with missing data for each variable of interest	-
Outcome data	15*	Report numbers of outcome events or summary measures	11-13

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	11-13
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	-
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12-13
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	16-17
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-17
Generalisability	21	Discuss the generalisability (external validity) of the study results	16-17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	18

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.