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Original Article

Detection and awareness of chronic renal insufficiency and related complications at a tertiary care hospital in China

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Abstract: Background: The prevalence of chronic renal insufficiency (CRI) has markedly increased in recent years worldwide, but the awareness remains low. In this cross-sectional study, we retrospectively investigated the detection and awareness of CRI and related complications at a tertiary care hospital in China. Methods: A total of 51,496 adult patients who were hospitalized at our hospital from October 2013 to December 2014 were included in this study. Demographics, clinical data, and laboratory data included urinary and hematologic parameters were collected. CRI was defined as estimated GFR (eGFR) <60 ml/min per 1.73 m^2, and patients with acute kidney injury were excluded. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) two-level race equation was used for reporting eGFR. Results: The subjects comprised 55.1% men and 44.9% women, the age was 68 (52-78) y. The overall prevalence of CRI was 4.1%. It was noted that there were about 64.8% CRI patients (excluded patients from nephrology department) being not diagnosed during their hospitalization. Among CRI patients, the prevalence of anemia, hypocalcaemia, hyperphosphatemia, and acidosis was 65.5%, 26.1%, 34.0% and 41.6% respectively, and the according prevalence increased significantly as renal function declined in patients without receiving dialysis. The total prevalence of hypertention and hyperkalemia was 54.5% and 9.9%, respectively, and rose by CKD stage. Conclusions: CRI and related complications were great burden in hospitalized patients, but the detection and awareness was still low. Future work is needed to organize a good management program to enable timely diagnosis and treatment of CRI and related complications.

Keywords: Chronic kidney disease, CRI-related complications, prevalence, awareness, treatment

Introduction

Chronic kidney disease (CKD) is increasing worldwide and has become a global public health problem [1]. It is reported that in USA, the prevalence of CKD was about 10.2% [2]. And in England, the prevalence of eGFR <60 ml/min/1.73 m^2 (defined as chronic renal insufficiency, CRI) was 5.2% [3]. Meanwhile, a recent national survey in China indicates that the prevalence of CKD was about 10.8%, and the prevalence of CRI was 1.7% in general population [4]. CKD has been associated with high morbidity and mortality [5], and the costs associated with the care of patients with end-stage renal disease were estimated to exceed US$1 trillion globally [6]. Meanwhile, CKD was ranked 36th in the list of causes of global years of life lost in 1990, but rose to 19th in 2013 [7]. Hence, it is important to launch programs aiming at reducing the burden of CKD.

CRI was significantly associated with increased risk of all-cause and cardiovascular mortality independently [8]. Early detection of CRI is necessary for delaying disease progression and preventing many associated chronic diseases, including cardiovascular disease and mineral and bone diseases [9, 10]. And also early identification of complications is also needed since anemia and hyperparathyroidism were observed in early CKD stages [11]. To our knowledge, the awareness of CKD remains low. A study in 32 general practices in England showed that

among the participants who met National Institute for Health and Clinical Excellence (NICE) criteria, 41% patients were unaware of their CKD diagnosis [12]. In Chinese adults, only 10.04% of the people who had CKD were aware of their CKD diagnosis [13]. Studies from Taiwan reported that the overall awareness of CKD was 3.5-9.7% [14]. Low awareness has also been noted among health-care providers. A Representative sample of 451548 Italian adults followed up by general practitioners showed that only 17.2% had undergone serum creatinine testing, and the age-adjusted prevalence of CRI was 9.33%, but only 15% had been correctly diagnosed [15]. A primary care-based cross-sectional study in Taian, China, reported that approximately 9.5% of the residents had CKD, the awareness of CKD was only 1.4% [16]. In another study of 39 525 hypertensive patients, 23% had CKD, but general practitioners diagnosed it correctly was only 3.9% [17]. Incorrect diagnosis results in missing of critical time for the treatment of kidney disease. Methods for screening the CRI is one fundamental strategy for the primary prevention of CKD, so, in this cross-sectional study, we retrospectively investigated the prevalence and complications of CRI at a tertiary care hospital in China.

Materials and methods

Study population

A total of 51496 adult patients (≥ 18 y) who were hospitalized in Qianfoshan Hospital, Shandong University from October 2013 to December 2014 were enrolled in the study. But patients with an increase in serum creatinine by ≥ 26.5 μmol/L (≥ 0.3 mg/dL) within 48 h or an increase in serum creatinine to ≥ 1.5 times baseline within the previous 7 days were excluded according the definition of acute kidney injury [18]. Patients with estimated GFR (eGFR) <60 ml/min/1.73 m^2 during this period were defined as CRI. Totally 2115 cases were entered into the final analysis, which included 1166 males and 949 females. The median age was 68 (52-78) y. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. The ethics committee of Qianfoshan Hospital approved the study. All of the participants gave written informed consent to take part in the study.

Blood biochemistry measurements and biometric parameters

Blood was collected by means of venipuncture after an overnight fast of at least 10 h. Serum creatinine was measured by the Roche enzymatic method on an automatic biochemistry analyzer (Roche P Modular with Roche Creatininase Plus assay, Hoffman-La Roche, Ltd., www.roche.com). And eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) two-level race equation [19]. Hemoglobin (Hb), blood urea nitrogen (BUN), serum uric acid (UA), Serum albumin (ALB), fasting blood-glucose (FBG), glycosylated hemoglobin, serum triglyceride (TG), high density lipoprotein (HDL), low density lipoprotein (LDL), proteinuria were measured by automatic biochemistry analyzer. Sociodemographic characteristics, health history (eg., hypertension, diabetes, and history of CKD), and lifestyle behavior (eg., smoking and drinking) were obtained by means of a questionnaire.

Assessment criteria

CRI was classified as 3A to 5 stages according to K/DOQI guideline [20], and patients who were receiving dialysis were defined as stage 5D. Anemia was diagnosed as the Hb concentration is <13.0 g/dL in male and <12.0 g/dL in female [21]. Hypertension (HTN) was defined as a mean systolic blood pressure of more than 140 mmHg or a mean diastolic blood pressure of more than 90 mmHg, or both, or patients already being prescribed by anti-hypertensive medicaments according to The American Heart Association [22]. Diabetes was defined as fasting blood glucose ≥ 7.0 mmol/L or by the use of hypoglycemic agents or by self-reported history of diabetes. The normal range of serum calcium and phosphorus were 2.09 to 2.54 mmol/L and 0.87 to 1.45 mmol/L, respectively. The optimal PTH levels was recommended to be 35-70 ng/L in stage 3, 70-110 ng/L in stage 4, 150-300 ng/L in stage 5, and 150-600 ng/L in stage 5d [23]; Metabolic acidosis was defined as plasma carbon dioxide combining power (CO2-CP) value <22 mmol/L1 and hyperkalemia as serum potassium >5.5 mmol/L.

Table 1. Comparison among stage 3A-5D CRI

Variables	Stage 3A (n=874)	Stage 3B (n=351)	Stage 4 (n=231)	Stage 5 (n=299)	Stage 5D (n=360)	*P* value
Age (y)	75 (63-81)	75 (62-92)	63 (51-76)	55 (41-70)	52 (41-65)	<0.001
Men (n, %)	462 (52.9)	195 (55.6)	135 (58.4)	158 (52.8)	216 (60.0)	0.14
Current Smocking (n, %)	220 (25.2)	94 (26.8)	60 (26.0)	60 (20.1)	78 (21.7)	=0.19
Current Drinking (n, %)	206 (29.7)	75 (21.4)	53 (22.9)	57 (19.1)	64 (17.8)	=0.16
History of CVD (n, %)	591 (67.6)	262 (74.6)	151 (65.4)	207 (69.2)	268 (74.4)	=0.01
Hypertension (n, %)	540 (61.8)	225 (64.1)	141 (61.0)	192 (74.25)	258 (71.7)	=0.02
Diabetes (n, %)	194 (22.2)	88 (25.1)	66 (28.6)	56 (18.7)	78 (21.7)	=0.07
Kidney disease (n, %)	41 (4.7)	36 (10.3)	43 (18.6)	25 (8.4%)	348 (96.7)	<0.001
Systolic BP (mmHg)	138.89±23.36	139.22±24.51	142.84±26.59	149.74±25.77	153.04±27.63	<0.001
Diastolic BP (mmHg)	79.01±13.95	78.1±13.68	81.9±15.36	88.26±17.4	89.67±15.98	<0.001
Hemoglobin (g/L)	124.87±22.42	116.31±24.35	101.97±26.07	92.14±24.31	101.47±23.9	<0.001
Serum creatinine (umol/L)	105.8 (92.1-118.6)	140.0 (122.3-158.9)	232.9 (201.7-273.4)	623.4 (434.5-930.0)	781.3 (597.7-999.5)	<0.001
Blood urea nitrogen (mmol/L)	7.7 (6.3-9.6)	10.8 (8.3-13.7)	16.0 (12.3-21.2)	27.8 (20.1-38.2)	24.4 (19.1-30.5)	<0.001
Cystatin C (mg/L)	1.48 (1.29-1.69)	1.85 (1.63-2.17)	2.65 (2.25-3.07)	4.18 (3.45-5.38)	5.88 (4.64-7.32)	<0.001
Serum uric acid (umol/L)	365.3 (301.3-431.8)	401.2 (338.6-483.3)	437.4 (354-523.6)	465.2 (372.9-582.6)	376.25 (311.2-446.5)	<0.001
Serum albumin (g/L)	38.74±6.04	36.6±6.22	34.20±6.93	35.07±6.77	37.8±6.24	<0.001
Serum potassium (mmol/L)	4.2 (3.88-4.5)	4.29 (3.91-4.63)	4.47 (3.97-5.02)	4.65 (4.15-5.31)	4.91 (4.30-5.60)	<0.001
Serum sodium (mmol/L)	140 (137.0-142.0)	140 (137-142)	139 (136-141.3)	138.0 (136.0-141.0)	139.0 (136.0-141.0)	<0.001
Serum calcium (mmol/L)	2.27±0.19	2.25±0.22	2.17±0.23	2.11±0.33	2.20±0.31	<0.001
Serum phosphorus (mmol/L)	1.14 (1.01-1.29)	1.17 (1.05-1.36)	1.3 (1.13-1.53)	1.8 (1.44-2.30)	1.79 (1.38-2.23)	<0.001
Venous CO_2-CP (mmol/L)	24.85±4.43	23.48±4.5	21.65±4.97	20.06±5.19	21.71±4.49	<0.001
Fasting blood-glucose (mmol/l)	5.45 (4.83-6.6)	5.42 (4.74-7.37)	5.32 (4.62-7.0)	5.13 (4.43-6.22)	4.70 (4.14-5.94)	<0.001
Glycosylated hemoglobin (mg/dL)	6.3 (5.75-7.55)	6.45 (5.73-7.80)	6.50 (5.50-8.00)	6.30 (5.35-8.15)	6.8 (5.95-9.08)	=0.21
Serum triglyceride (mmol/L)	1.19 (0.92-1.76)	1.25 (0.96-1.82)	1.23 (0.9-0-1.85)	1.38 (0.99-1.98)	1.34 (0.92-1.79)	<0.001
High density lipoprotein (mmol/L)	1.17±0.36	1.11±0.37	1.05±0.34	1.04±0.50	1.13±0.34	<0.001
Low density lipoprotein (mmol/L)	2.79±0.96	2.58±0.98	2.52±0.97	2.61±1.13	2.44±0.83	<0.001
eGFR (ml/min/1.73 m^2)	54.12 (50.23-57.36)	38.78 (34.59-42.08)	22.23 (18.32-25.90)	6.62 (4.58-10.59)	5.50 (4.28-7.34)	<0.001

CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate.

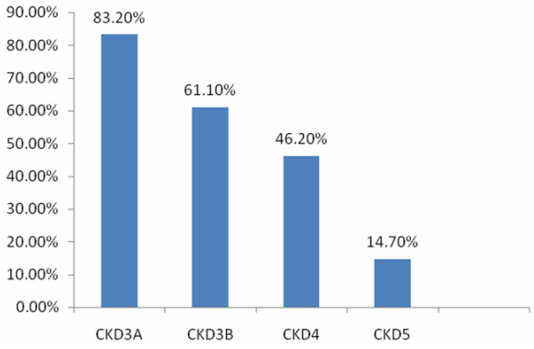

Figure 1. Undiagnosed percent of different CKD stage in none nephrology department.

Statistical analysis

Excel charts were used to establish case files database and those data were processed by using SPSS v17.0 statistical software (Chicago, IL). Data were presented as the mean ± SD (normally distributed continuous variables) or percentage (non-normal distribution parameters), one way ANOVA was used to compare means for normally distributed continuous variables, non-parametric test was used to compare non-normal distribution parameters, counting variables was compared by chi-squared test. Two-tailed *P* value <0.05 was considered statistically significant.

Results

Prevalence of CRI

In this study, the overall prevalence of CRI was 4.1% (2115/51496). CRI was respectively distributed from stage 3A to stage 5D at the following percentage, 41.3% (stage 3A), 16.6% (stage 3B), 10.9% (stage 4), 14.1% (stage 5) and 17.0% (stage 5D) (**Table 1**). The proportion of stage 3 patients was the largest population in definite CRI. There were 598 patients (28.3%) come from nephrology department. It was worthy to note that there were about 64.8% patients in the deparments other than nephrology department, which had been not diagnosed with CRI during their hospitalization across all stages: 83.2% in stage 3A, 61.1% in stage 3B, 46.2% in stage 4, 14.7% in stages 5, 2.6% in stage 5D (**Figure 1**).

Complications

Anemia and acidosis: Among CRI patients, the prevalence of anemia and acidosis was 65.5% and 41.6% respectively, and increased significantly in stage 3a-5, but decreased in stage 5d (**Table 2**). Meanwhile, the overall usage rate of erythropoietin (EPO) among anemic patients was 42.3%, and raised with the progress of disease (**Figure 2**), the overall usage rate of acidosis drug among acidosis patients was 54.2%, and also raised as the CRI worsen (**Figure 3**).

Mineral and bone disorder (MBD): Serum phosphorus increased sharply and serum calcium decreased obviously along with the renal function declined. According to the K/DOQI guideline, the total prevalence of hypocalcaemia and hyperphosphatemia was 26.1% and 34.0% respectively, which all increased significantly in stage 3A-5, but decreased in stage 5D (**Table 2**). There were only 611 patients have PTH testing, among them, the patients with high PTH levels varied by stage 3A to 5D (**Table 2**). Besides, the proportion of cases that had calcium supplements to improve hypocalcaemia was 55.6%, raised in stage 3B to 5D (**Figure 4**).

Hyperkalemia and hypertension: The total prevalences of hypertension and hyperkalemia were 54.5% and 9.9%, respectively. And the prevalence of complications increased significantly along with GFR decline (**Table 2**).

Discussion

CKD is an increasing public health issue and the awareness remains low [1]. A research utilized 2000-2009 data from the National Kidney Foundation's Kidney Early Evaluation Program showed that of 109,285 participants, 26% had CKD disease defined by albuminuria or eGFR <60 mL/min/1.73 m^2, only 9% reported being aware of kidney disease [24]. Low awareness has also been noted among health-care providers. Incorrect diagnosis lead to be delayed recourse to nephrologists, which leads to missed opportunities to implement strategies in time for slowing disease progression and treating complications. In this retrospective study, the overall prevalence of CRI was 4.1%, while the proportion of stage 3 was 57.9%. A cohort study of patients with early CKD showed that the rate of kidney function decline was associated with a higher risk of hospitalizations, readmissions, and prolonged length of hospital stay [25]. There were about 64.8% patients in none nephrology department being

Table 2. Prevalence of complications in the cohort

Complication		Stage 3A	Stage 3B	Stage 4	Stage 5	Stage 5D	*P* value
Anemia (n, %)	Prevalence	385 (45.2)	225 (65.0)	183 (82.1)	262 (90.3)	301 (84.1)	<0.05
Serum Calcium (mmol/L) (n, %)	<2.09	104 (14.3)	58 (19.2)	74 (34.9)	135 (46.9)	122 (34.2)	<0.05
	2.09-2.54	592 (81.3)	226 (74.8)	136 (64.2)	135 (46.9)	201 (56.3)	<0.05
	>2.54	32 (4.4)	18 (19.2)	2 (0.9)	18 (6.25)	34 (9.5)	<0.05
Serum Phosphatemia (mmol/L) (n,%)	<0.87	76 (11.3)	21 (7.5)	7 (3.5)	9 (3.4)	13 (3.9)	<0.05
	0.87-1.45	543 (80.9)	209 (74.6)	127 (64.1)	60 (22.7)	88 (26.3)	<0.05
	>1.45	52 (7.7)	50 (17.9)	64 (32.3)	195 (73.9)	233 (69.8)	<0.05
High PTH (N, %)		5 (10.2)	12 (35.3)	22 (24.7)	55 (31.8)	29 (10.9)	<0.05
Serum kalemia (mmol/L) (n, %)	<3.5	73 (9.4)	35 (10.8)	20 (9.1)	21 (7.2)	14 (3.9)	<0.05
	3.5-5.5	696 (89.6)	280 (86.7)	177 (80.8)	214 (73.8)	242 (67.8)	<0.05
	>5.5	8 (0.9)	8 (2.5)	22 (10.0)	55 (19.0)	101 (28.3)	<0.05
Venous CO_2-CP (mmol/L) (n, %)	<22	147 (22.8)	88 (33.8)	109 (54)	186 (66.0)	195 (54.9)	<0.05
	22-34	482 (74.8)	170 (65.4)	92 (45.5)	95 (33.7)	158 (44.5)	<0.05
	>34	15 (2.3)	2 (0.8)	1 (0.5)	1 (0.4)	2 (0.6)	<0.05
Hypertension (n, %)		408 (47.2)	158 (45.9)	122 (53.7)	197 (66.8)	254 (71.3)	<0.05

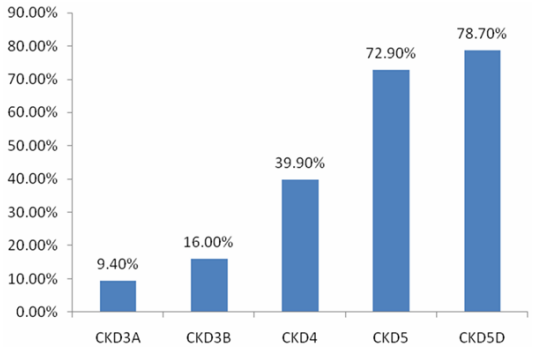

Figure 2. The treatment percent by erythropoietin (EPO) among anemic patients.

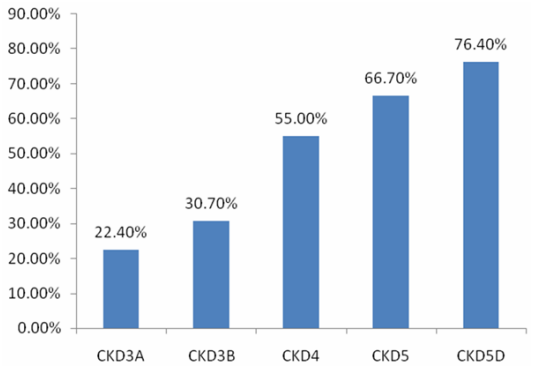

Figure 3. Proportion of acidosis drug application among acidosis patients.

undiagnosed with CRI during their hospitalization, which raised a very important issue for public health standpoint, and also for individual hospitalized patients. The Undiagnosed patients mainly concentrated in stage 3a (83.2%) and stage 3b (61.1%), possibly because precise diagnose of less symptomatic or asymptomatic early-stage chronic kidney disease was difficult, and those patients often referred to doctors for other reasons.

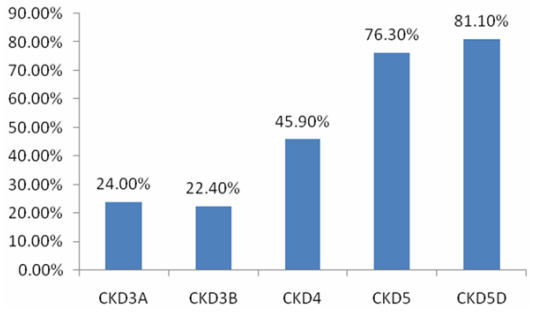

Figure 4. Proportion of Calcium supplements application among hypocalcaemia patients.

The diagnosis of CRI is of paramount importance, and related complications also cannot be ignored. Renal anemia is a common complication of CKD and is a significant risk factor of cardiovascular disease and aggravates decrease of life quality. An abroad survey showed that more than 40% of patients with CKD are anemic, and a significant proportion of population was under-recognized and undertreated [26]. In our study, the prevalence of anemia among CRI patients was 65.5%, and increased by stage. Meanwhile, since the primary cause of anemia is the inadequate production of erythropoietin by the kidneys to support eryth-

ropoiesis [27], the application of erythropoietin (EPO) is increased by stage. Anemia occurs in early CKD stage [11], and may increase by stage with CKD progress, patients nutrition problems and complications appearance or aggravation, but the prevalence of dialysis patients with anemia decreased may as a result of the use of erythopietin and the clearness of toxic inhibitors of erythropoiesis. The treatment of renal anemia cannot be ignored; a survey showed that renal anemia was associated with a more rapid evolution of CKD and a higher risk of cardiovascular events and hospitalization in non-dialysis-dependent CKD patients [28]. And research also showed that the early initiation of erythropoiesis-stimulating agents' therapy could be more effective at reducing the risk of renal events in nondialysis CKD patients with anemia [29]. But in our study, the overall rate of treatment was only 42.3%, and the early utility was low, so it is necessary to identify the anemia in CRI patients and prevention and management strategies should be adopted early. Metabolic acidosis has also been shown to be a risk factor in the progression of renal dysfunction [30, 31], which can impact chronic kidney disease (CKD) through many ways such as direct renal damage [32, 33], metabolic bone disease [34]. Therefore, correction of metabolic acidosis has the protection of renal function, sodium bicarbonate supplementation as a relatively cheap treatment option is of urgent need to develop a proper treatment strategy for those patients [35]. In this article, the total prevalence acidosis was 41.6%, and as the renal disfunction progressing, the prevalence rate increased significantly. Meanwhile, the percentage of patients who had oral or intravenous drug to correct acidosis rose by stage. But the total usage of drug among acidosis patients was only 54.2%, and attention should be attached.

As the kidney function decreasing, there is a progressive deterioration in mineral homeostasis, such as the disruption of normal serum concentrations of phosphorus and calcium, and parathyroid hormone. Bone abnormalities are found almost universally in patients with CKD requiring dialysis (stage 5D), and in the majority of patients with CKD stages 3-5 [23]. In our study, the total prevalence of hypocalcaemia and Hyperphosphatemia was 26.1%, and 34.0% respectively, increased by stage. Blood phosphorus levels decreased due to dialysis treatment, and the Calcium supplements improved hypocalcaemia. There were 611 patients have PTH testing, among them, the prevalence of patients with high PTH were not raised as renal function changed. We think this may be related to the small sample size. Hyperphosphatemia is an inevitable clinical consequence of the ESRD. The epidemiological evidence suggesting that hyperphosphatemia is an important risk factor [36]. Another survey showed that while the risk of death increased 18% for every 1 mg/dl increase in serum phosphorus [37]. These observational data suggest that it is needed to control serum phosphorus in patients with CKD. The guidelines also concluded that both calcium carbonate and calcium acetate were effective in lowering serum phosphorus, but both were associated with hypercalcemia and gastrointestinal side effects. Our research indicated that the proportion of cases that had calcium supplements to improve the calcium and phosphorus metabolism disorder was 55.6%, raised in stage 3b to 5d.

The complications of CRI also include potassium imbalances and Hypertension. Hyperkalemia is also not allow to be ignored as kidney regulate potassium homeostasis by transporting and regulating potassium secretion, reabsorption and excretion [38]. The risk of hyperkalemia is increased with CKD progressing [39], and the prevalence of hyperkalemia increases from 2 to 42%, when eGFR decreases from above 60 to below 20 ml/min/1.73 m^2 [11]. Studies also suggested that hyperkalemia is associated with increased risk of ESRD in CKD population [40]. Our article showed the total prevalence of hyperkalemia was 9.9% and as the CRI progressing, the prevalence rate increased significantly, which indicates that hyperkalemia needs to be given increased attention. Hypertension (HTN) is a commonly reported cause of CKD. In contrast, chronic renal insufficiency can lead to HTN among previously normotensive patients. A nationwide, multicenter study in China showed that the prevalence of hypertension in non-dialysis CKD patients was 67.3%, and the hypertension control was suboptimal, with successive CKD stages, the risk of uncontrolled hypertension increased [41]. While in hemodialysis (HD) patients, HTN prevalence reach up to more

than 80%, most of whom have isolated systolic or combined systolic and diastolic HTN [42]. In our study, the prevalence of HTN among CRI patients was 54.5%, and increased by stage. HTN is an important risk factor for left ventricular hypertrophy, cardiovascular events, and stroke [43]. Moreover, blood pressure lowering treatment was associated with lower risks of cardiovascular events [42]. In short, hypertension deserves as much attention to make great efforts to solve.

The study has several limitations. First, the patients enrolled may not be representative of the overall population as a single-center study. Second, patients at stage 1-2 were excluded from this cohort, so we could not evaluate complications at this early CRI stage. Third, the information of a small number patients was not well established, especially the clinical test results, which may lead to a certain error in the results. Finally, this cross-sectional analysis cannot expressly demonstrate cause-and-effect relations between the clinical factors and the complications.

In conclusion, this study demonstrated that CRI is a great burden in the hospital, and awareness was still low. Future work is needed to explore how to organize a good management program to enhance the care of patients with CKD. Its related complications should not be ignored and the use of accurate methods to enable timely diagnosis is needed.

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Disclosure of conflict of interest

None.

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