Prevalence and risk factors for kidney disease in Chinese HIV-Infected patients: A cross-sectional study

Naxin Zhao

Beijing Ditan Hospital, Capital Medical University, China

Pan Xiang

Beijing Ditan Hospital, Capital Medical University, China

Zhili Zeng

Beijing Ditan Hospital, Capital Medical University, China

Hongyuan Liang

Beijing Ditan Hospital, Capital Medical University, China

Fang Wang

Beijing Ditan Hospital, Capital Medical University, China

Jiang Xiao

Beijing Ditan Hospital, Capital Medical University, China

Di Yang

Beijing Ditan Hospital, Capital Medical University, China

Meiling Chen

Beijing Ditan Hospital, Capital Medical University, China

Guiju Gao (✉ guiju.gao@163.com)

Beijing Ditan Hospital, Capital Medical University, China

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Abstract

Background

Kidney disease is an important comorbidity in HIV-infected patients, and is associated with poor outcomes of these patients. However, data on kidney function in Chinese HIV-Infected patients are scarce. In this study we determined the prevalence of kidney disease in PLWH involving ART-naïve patients and ART-experienced patients in China and explored its associated risk factors.

Methods

In the cross-sectional study, we recruited hospitalized adult HIV-infected patients. Demographic characteristics, clinical information and laboratory variables were collected. Kidney disease was defined as $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$, hematuria, proteinuria, or microalbuminuria. We calculated the prevalence of kidney disease and used logistic regression to assess its associated risk factors.

Results

A total of 501 Chinese adult HIV-infected patients were enrolled, with 446 (89.0%) male and 55 (11.0%) female. Median age was 39 (IQR 30–50) years old. The prevalence of kidney disease was 19.0%. 22 (4.4%) patients had $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$, 53 (10.6%) patients had hematuria, 11 (2.2%) patients had proteinuria, 40 (8.0%) patients had microalbuminuria. Using univariate analysis, kidney disease was found to be significantly associated with older age, hypertension, diabetes mellitus, duration of HIV, ART and its duration, TDF-containing regimen, HIV viral load $< 20 \text{ copies/mL}$, lower hemoglobin and albumin, higher UA, CRP, CHOL and TG. In the multivariate logistic regression analysis, older age (OR 1.031, 95%CI: 1.006–1.058, $P = 0.016$), diabetes mellitus (OR 3.699, 95%CI: 1.388–9.860, $P = 0.009$) and Anemia (hemoglobin OR 0.970, 95%CI: 0.954–0.986, $P = 0.000$) were significantly associated with kidney disease.

Conclusions

The prevalence of kidney disease in HIV-infected patients in China is high. It is very important to monitor renal function and comprehensively manage the various risk factors in these people. Especially, there is an urgent need to study antiretroviral drugs with no or less nephrotoxicity and with the ability to prevent the virus from depositing in the kidney to protect renal function of HIV-infected patients.

Background

Kidney disease is an important comorbidity in human immunodeficiency virus (HIV) infected patients and is associated with poor outcomes of these patients^[1–3, 4]. Lene Ryom et al. ^[5] reported kidney dysfunction

lead to increased morbidity and mortality in HIV-infected patients. The prevalence of renal dysfunction in HIV-infected individuals varies from 11.8–76.6% depending on different subjects and definition of renal impairment^[6, 7].

Prior studies indicated contributing factors to renal impairment are older age, hypertension, diabetes mellitus, hepatitis B virus and hepatitis C virus infections, worse virological control, low CD4 count and nephrotoxic drugs in people living with HIV (PLWH)^[8, 9]. Tenofovir disoproxil fumarate (TDF) is widely used as a first line antiretroviral treatment (ART) which was suspected to be associated with renal impairment^[10, 11].

However, data on kidney function in Chinese HIV-Infected patients are scarce. The aim of our study was to determine the prevalence of kidney disease in PLWH involving ART-naïve patients and ART-experienced patients in China and identify its associated risk factors.

Methods

Study design and participants

We conducted a cross-sectional study on HIV-infected adults. All HIV-infected patients above 18 years old who admitted to Department of Infectious Diseases, Beijing Ditan Hospital, Capital Medical University from February 2019 to January 2020 were observed. Exclusion criteria were (1) Pregnant women, participants who were suffering from urinary tract infection, patients who had urinary tumor, renal tuberculosis, kidney stones or other obstructive nephropathy; (2) The patients who had missing data which is essential to identify if there is kidney damage.

This study was approved by the Ethics Committee of Beijing Ditan Hospital, Capital Medical University. The approval numbers is Jdlkz 2019-056-02. We obtained informed consent from each participant.

Data collection and definitions

Demographic characteristics, clinical information and laboratory variables were collected from electronic medical records, including the following parameters: sex, age, weight, height, hypertension, diabetes mellitus, hepatitis B virus (HBV) co-infection, hepatitis C virus (HCV) co-infection, Syphilis, tumor, duration of HIV, antiretroviral regimen and duration, plasma HIV viral load, CD4+ T-cell count, serum creatinine, urine protein, urine microalbumin, serum concentration of hemoglobin (Hb), albumin (Alb), uric acid (UA), homocysteine (Hcy), procalcitonin (PCT), C reactive protein (CRP), triglycerides (TG), total cholesterol (CHOL), high density lipoprotein cholesterol (HDL) and low density lipoprotein cholesterol (LDL). Body-mass index (BMI) was calculated (kg/m^2). Serum creatinine was measured at Clinical Laboratory Department in Beijing Ditan Hospital, Capital Medical University using enzymatic assay. The estimated glomerular filtration rate (eGFR) was calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equations^[12] (Table 1).

Table 1 CKD-EPI creatinine equations for eGFR

Gender	Scr (mg/dL)	Equation for eGFR(mL/min/1.73 m ²)
female	≤0.7	$141 \times (\text{Scr}/0.7)^{-0.329} \times 0.993^{\text{age}} \times 1.018$
	>0.7	$141 \times (\text{Scr}/0.7)^{-1.209} \times 0.993^{\text{age}} \times 1.018$
male	≤0.9	$141 \times (\text{Scr}/0.9)^{-0.411} \times 0.993^{\text{age}}$
	>0.9	$141 \times (\text{Scr}/0.9)^{-1.209} \times 0.993^{\text{age}}$

Scr: serum creatinine; eGFR: estimated glomerular filtration rate.

Patients with the presence of $\geq +1$ protein or $\geq +1$ occult blood on a spot urine specimen was defined as abnormality on urine dipstick. To minimize the influence of urine sample contamination, those patients who had abnormal urinalysis will be arranged to take a new urine specimen for repeating urine assay. Therefore, patients who showed $\geq +1$ protein or $\geq +1$ occult blood on urine specimen twice consecutively were defined as proteinuria or hematuria respectively. Urine microalbumin was measured using immunoturbidimetry with normal reference range <1.9 mg/dL. Patients who showed ≥ 1.9 mg/dL for urine microalbumin twice consecutively were defined as microalbuminuria.

Patients with one of the following characteristics were considered to have kidney disease: eGFR < 60 mL/min/1.73 m², hematuria, proteinuria, or microalbuminuria.

Statistical analysis. All analyses were performed using Statistical Package for Social Sciences (SPSS) 20.0 software (SPSS Institute, Chicago IL, USA). We conducted One-Sample Kolmogorov-Smirnov test for homogeneity of quantitative data. We presented data with normal distribution as mean±standard deviation (SD), including BMI, Alb and LDLC. Data with abnormal distribution was presented as median (interquartile range), including age, duration of HIV, antiretroviral duration, plasma HIV viral load, CD4 T-cell count, serum creatinine, Hb, UA, Hcy, PCT, CRP, TG, CHOL and HDLC. Categorical variables were presented as frequency and percentage. Demographic characteristics, clinical information and laboratory variables were compared between the two groups of patients who suffered and did not suffer from kidney disease. A Student's *t*-test, Wilcoxon signed rank test and chi-squared test was used where appropriate. Univariate and multivariate logistic regression analyses were carried out to estimate associations between potential risk factors and the development of kidney disease. A two-tailed *P* values <0.05 were considered statistically significant.

Results

A total of 563 patients with HIV were admitted to Department of Infectious Diseases, Beijing Ditan Hospital, Capital Medical University during the study period. Of whom 62 (11.01%) were excluded for the following reasons: 4 patients were younger than 18 years old, 8 patients showed kidney stones, 1

patient had right renal tuberculosis, 1 patient suffered from lymphoma with left renal pelvis and calyces invaded, 1 patient showed left upper ureteral dilatation, and 47 individuals with $\text{eGFR} \geq 60 \text{ mL/min/1.73 m}^2$ had missing data for urine test, leading to impossibility to identify whether they had kidney disease. Finally, 501 (88.99%) Chinese adult HIV-infected patients were enrolled (Fig. 1).

Patient characteristics. There were 446 (89.0%) male and 55 (11.0%) female patients. Median age was 39 (IQR 30–50) years old, and the youngest patient was 19 years old, while the oldest one was 83 years old. Mean BMI was $21.65 \pm 3.57 \text{ kg/m}^2$. HBV, HCV and Syphilis existed in 33 (6.6%), 16 (3.2%), and 139 (27.7%) patients, respectively. 40 (8%), 39 (7.8%), and 37 (7.4%) patients had hypertension, diabetes, and tumor, respectively. Median duration of HIV was 8 (IQR 0–57.5) months.

The longest duration of HIV was 276 months. 153 (30.5%) patients were newly diagnosed with HIV infection (diagnosed within 1 month). 297 (59.3%) patients were receiving antiretroviral therapy, of whom 239(47.7%) patients were receiving TDF-containing regimen. The majority of these patients (165, 32.9%) were prescribed ART with a combination of TDF, lamivudine (3TC), and efavirenz (EFV). Median duration of ART was 1 (IQR 0–18) month. The longest duration of ART was 216 months.

162 (36.3%) patients had HIV viral load $<20 \text{ copies/mL}$ or undetectable. Median CD4^+ T cell count was 106 (IQR 28.5–362) cells/ μL , with 308 (61.5%) patients presenting with a CD4^+ T cell count $<200 \text{ cells}/\mu\text{L}$. More information are showed in Table 2.

Table 2. Demographic and clinical characteristics of participants

	Total n=501	No Kidney Disease n=406	Kidney Disease n=95	P
Age, median (IQR), y	39 (30–50)	36 (30–47)	47 (37–56)	0.000
Gender, No. (%)				0.363
Male	446(89.0%)	364(89.7%)	82(86.3%)	
Female	55(11.0%)	42(10.3%)	13(13.7%)	
BMI, Mean±SD, kg/m ²	21.65±3.57	21.54±3.54	22.15±3.67	0.147
HBV coinfection, No. (%)	33(6.6%)	29(7.1%)	4(4.2%)	0.300
HCV coinfection, No. (%)	16(3.2%)	11(2.7%)	5(5.3%)	0.201
Syphilis, No. (%)	139(27.7%)	116(28.6%)	23(24.2%)	0.446
Hypertension, No. (%)	40(8%)	20(4.9%)	20(21.2%)	0.000
Diabetes mellitus, No. (%)	39(7.8%)	19(4.7%)	20(21.1%)	0.000
Tumor, No. (%)	37(7.4%)	29(7.1%)	8(8.4%)	0.664
duration of HIV, Median (IQR), mo	8 (0–57.5)	7 (0–48)	12 (1–72)	0.043
duration of ART, Median (IQR), mo	1 (0–18)	1 (0–12)	3 (0–39)	0.016
HIV viral load, median (IQR), copies/mL	2239 (0– 167717)	14030(1– 188480)	46(0–30485)	0.001
<20 copies/mL, No. (%)	162(32.3%)	120(29.9%)	42(45.2%)	0.007
≥20 copies/mL, No. (%)	333(66.5%)	282(70.1%)	51(54.8%)	
CD4 count, Median (IQR), cells/uL	106 (28.5–362)	96 (22–336)	159(69–431)	0.002
<200 cells/ uL, No. (%)	308(61.5%)	256(63.1%)	52(54.7%)	0.16
≥200 cells/ uL, No. (%)	198(38.5%)	150(36.9%)	43(45.3%)	
ART-naïve, No. (%)	204(40.7%)	176(43.3%)	28(29.5%)	0.015
TDF-containing regimen, No. (%)	239(47.7%)	188(81.7%)	51(76.1%)	0.299
eGFR, median (IQR), mL/min/1.73 m ²	115 (103–124)	116 (105–125)	105 (76–119)	0.000
Hb, median (IQR), (g/L)	122 (105–137)	125 (107–139)	115 (93–127)	0.000
UA, median (IQR), (umol/L)	298 (231–394)	296 (231–386)	318 (231–468)	0.103

ALB, Mean±SD, (g/L)	36.1±5.9	36.4±5.9	34.7±5.4	0.013
Hcy, median (IQR) , (umol/L)	12.58 (9.75–16.89)	12.65 (9.80–16.72)	12.01(9.63–18.45)	0.777
PCT, median (IQR), (ng/mL)	0 (0–0.14)	0 (0–0.12)	0.06 (0–0.22)	0.001
CRP, median (IQR), (ng/L)	8.0 (1.4–37.3)	7.8 (1.4–35.8)	9.7 (1.2–54.1)	0.238
CHOL, median (IQR), (mmol/L)	3.50 (2.88–4.13)	3.47 (2.85–4.08)	3.64 (3.04–4.36)	0.036
TG, median (IQR), (mmol/L)	1.29 (0.88–2.01)	1.25 (0.88–2.02)	1.47 (0.88–2.01)	0.359
HDLc, median (IQR), (mmol/L)	0.70 (0.56–0.88)	0.71 (0.57–0.87)	0.70 (0.56–0.92)	0.806
LDLC, Mean±SD, (mmol/L)	2.13±0.76	2.13±0.74	2.15±0.83	0.776

IQR: interquartile range; BMI: Body-mass index; SD: standard deviation; HBV: hepatitis B virus; HCV: hepatitis C virus; HIV: human immunodeficiency virus; ART: antiretroviral treatment; TDF: tenofovir disoproxil fumarate; eGFR: estimated glomerular filtration rate; Hb: hemoglobin; UA: uric acid; ALB: albumin; Hcy: homocysteine; PCT: procalcitonin; CRP: C reactive protein; CHOL: total cholesterol; TG: triglycerides; HDLC: high density lipoprotein cholesterol; LDLc: low density lipoprotein cholesterol. The P values in bold are statistically significant P values.

Prevalence of renal dysfunction. Of the total study population, 95 patients had kidney disease. Therefore, the prevalence of kidney disease was 19.0%. 22 (4.4%) patients had eGFR < 60 mL/min/1.73 m², 53 (10.6%) patients had hematuria, 11 (2.2%) patients had proteinuria, 40 (8.0%) patients had microalbuminuria. Some patients have two or more of the four items at the same time, so the total number is not equal to 95. The ART-experienced patients had a higher prevalence of renal disease than the ART-naïve patients (22.6% vs 13.7%, $P = 0.013$). Participants with kidney disease showed lower HIV viral load and higher CD4+ T cell count. Participants with kidney disease were older, had a longer duration of HIV infection and ART, and were more likely to have hypertension and diabetes than those with no kidney disease. Procalcitonin and total cholesterol were higher while hemoglobin and albumin were lower in those with kidney disease than those with no kidney disease. More details were shown in table 2.

Association between renal function and Potential risk factors. Table 3 shows the strength of associations between kidney disease and its potential risk factors. Using univariate analysis, kidney disease was found to be significantly associated with older age, hypertension, diabetes mellitus, duration of HIV, ART and its duration, TDF-containing regimen, HIV viral load < 20 copies/mL, lower hemoglobin and albumin, and higher UA, CRP, CHOL and TG. There was no significant association between kidney disease and gender, BMI, HBV coinfection, HCV coinfection, Syphilis, tumor, CD4+ T cell count, PCT, HCY, HDLC or LDLc. In the multivariate logistic regression analysis, older age (OR 1.031, 95%CI: 1.006–1.058, $P =$

0.016), diabetes mellitus (OR 3.699, 95%CI: 1.388–9.860, $P = 0.009$) and Anemia (hemoglobin OR 0.970, 95%CI: 0.954–0.986, $P = 0.000$) were significantly associated with kidney disease.

Table 3. Logistic Regression Analysis for Identification of Predictors of Renal Impairment

	Univariate Model Unadjusted OR 95%CI	P	Multivariate Model Adjusted OR 95%CI	P
Age	1.053 1.034-1.073	0.000	1.031 1.006-1.058	0.016
Female	1.374 0.705-2.676	0.350	0.547 0.212-1.412	0.213
BMI	1.048 0.984-1.116	0.148	1.084 0.996-1.181	0.062
HBV coinfection	0.589 0.201-1.720	0.333	0.584 0.166-2.058	0.403
HCV coinfection	1.995 0.676-5.884	0.211	0.775 0.174-3.460	0.739
Syphilis	0.799 0.476-1.339	0.393	0.761 0.373-1.553	0.452
Hypertension	5.147 2.641-10.031	0.000	1.523 0.548-4.238	0.420
Diabetes mellitus	5.432 2.766-10.666	0.000	3.699 1.388-9.860	0.009
Tumor	1.195 0.528-2.705	0.668	0.685 0.240-1.954	0.479
duration of HIV	1.005 1.001-1.009	0.010	1.000 0.991-1.008	0.925
duration of ART	1.011 1.005-1.017	0.000	1.012 0.998-1.025	0.096
HIV viral load	1.000 1.000-1.000	0.728	1.000 1.000-1.000	0.564
≥20 copies/mL	0.517 0.326-0.819	0.005	0.934 0.398-2.189	0.874
CD4 count	1.000 1.000-1.001	0.115	1.000 0.999-1.001	0.820
≥200 cells/ uL	1.411 0.899-2.217	0.135	1.159 0.489-2.747	0.738
ART-experienced	1.831 1.130-2.967	0.014	2.253 0.641-7.921	0.205
TDF-containing regimen	1.200 1.018-1.414	0.030	1.761 0.689-4.496	0.237
Hb	0.980 0.971-0.989	0.000	0.970 0.954-0.986	0.000
PCT	0.064 0.994-1.138	0.072	1.052 0.984-1.125	0.136
UA	1.002 1.000-1.003	0.021	1.001 1.000-1.003	0.146
ALB	0.953 0.918-0.990	0.013	0.968 0.900-1.041	0.384
HCY	0.996 0.974-1.018	0.712	0.991 0.963-1.020	0.536
CRP	1.005 1.001-1.010	0.019	1.003 0.996-1.010	0.419
CHOL	1.293 1.065-1.571	0.009	2.112 0.784-5.689	0.139
TG	1.115 1.001-1.243	0.048	0.892 0.668-1.192	0.441
HDLC	1.824 0.902-3.688	0.095	1.539 0.331-7.162	0.583
LDLC	1.044 0.777-1.402	0.776	0.414 0.141-1.214	0.108

CI: confidence interval; OR: odds ratio; see table 2.

Discussion

In this study, we assessed the prevalence of kidney disease in Chinese adult HIV-infected patients and determined the associated risk factors of kidney disease in these people. Similar to previous studies^[6, 13], our study demonstrated that the prevalence of kidney disease among Chinese adult HIV-Infected patients was 19.0%. Furthermore, our present study showed a prevalence of kidney disease among ART-naïve patients of 13.7% and 22.6% among ART-experienced patients. This is in line with what is reported from a study among PLWH in Cameroon ^[6]. Kedar Joshi et al. ^[10] discovered a decrease in renal function in HIV-infected adults in Asia with long-term antiretroviral therapy, which is in line with our study. There is an urgent need to improve access to less nephrotoxic antiretrovirals.

Majority of the ART-experienced patients received TDF-containing regimen. The influence of TDF to the occurrence of kidney disease is still controversial. Using univariate analysis in our study, kidney disease was found to be associated with TDF-containing regimen, which is in line with some findings^[14–17]. But a study in the USA^[18] revealed that TDF-containing regimens did not lead to an increasing of the odds of kidney disease in those with low risk of chronic kidney disease (CKD).

Ying Cao et al. ^[13] determined the prevalence of CKD in Chinese HIV-infected ART-naïve patients was 16.1%, and they ascertained that advancing age and higher viral load were significantly correlated with CKD in these patient in 2013. Similar to what they founded, we determined the prevalence of kidney disease in PLWH in China was high and older age was significantly correlated with kidney disease. But we found participants with kidney disease showed lower HIV viral load in our study, which is inconsistent with them. The possible reasons are as follows: ART-experienced patients had lower viral load, but drug-related kidney damage occurred in them. This can also explain why CD4 cell count is higher in patients with renal damage in our study, while prior study^[9, 14, 19] confirmed low CD4 count was risk factor for kidney damage. Perhaps drug-related renal damage is more significant in Chinese population.

Kidney disease is an important complication of HIV. Several mechanisms may contribute to kidney injury in PLWH, including direct intrarenal HIV infection, comorbidities, and co-infections, immune dysregulation and treatment toxicity^[20]. Recent studies in HIV-infected kidney transplant recipients have emphasized that perhaps the kidney serves as a reservoir for virus^[21, 22]. The study in France^[21] discovered that HIV can infect kidney allografts despite undetectable viremia in HIV-infected recipients. This can also partly explain why did participants with kidney disease show lower HIV viral load in our study. Although the HIV virus in peripheral blood is effectively suppressed, the kidney is persistently damaged by the HIV virus which deposited in the kidney. It is necessary to study drugs that can prevent the virus from depositing in the kidney to protect renal function of HIV-infected patients.

Eduardo Shahar et al.^[11] reported co-infection with HCV is significantly associated with the decline in kidney function among HIV-infected patients. Amanda Mocroft et al.^[23] also found the odds of CKD were

increased in participants with HBV or HCV in HIV-positive individuals. But there was no significant association between kidney damage and HBV or HCV- coinfection in our study. The reason may be that the number of patients with HBV or HCV in our study is relatively small.

Consistent with previous studies^[24, 25], hemoglobin and albumin were lower in patients with kidney disease than those with no kidney disease in our study. Lin Pu et al.^[24] reported that patients with severe acute kidney injury (AKI) had lower serum albumin and hemoglobin levels among HIV-infected individuals. A study in the United States^[25] found lower serum albumin levels were strongly associated with kidney function decline in HIV-infected women independent of albuminuria, HIV disease status, and body mass index.

Our study find that kidney disease is significantly associated with hypertension, diabetes mellitus, duration of HIV, ART ,CRP, and CHOL, which is in line with prior researches^[26–29]. A study in Japan^[26] showed significant associations between kidney dysfunction and cholesterol, the coexistence of diabetes and hypertension. A retrospective cohort study involving 3714 HIV-infected patients^[27] identified older age, longer time with HIV infection, hypertension, increased total cholesterol levels, and being treated with ART as associated with renal impairment over time. Alison G Abraham et al.^[28] indicated that increases in total cholesterol may be a contributing factor for kidney damage in HIV-infected men. Minoru Ando et al.^[29] discovered that kidney tubular damage were characterized by advanced age, high C-reactive protein and coexisting diabetes mellitus. Through all these studies, we can see that the risk factors of kidney damage are various, so it is very important to monitor the renal function and comprehensively manage the risk factors in HIV population.

Our study has following advantages. Firstly, we used enzymatic method to quantify serum creatinine, which is more accurate than Jaffe method^[30]. Secondly, this is the first clinical study to determine the prevalence and correlative factors of kidney disease in PLWH involving ART-naïve patients and ART-experienced patients in China. Thirdly, we detected urine microalbumin to find patients with early renal damage.

Our study also has limitations. Firstly, we used CKD-EPI creatinine equations to calculate eGFR, which may underestimate the prevalence of renal dysfunction compared to CKD-EPI creatinine-cystatin C equations^[31]. Secondly, this is a single-center study, which largely limits its generalizability. Thirdly, the sample size is relatively small. A prospective larger scale multi-center study to determine the prevalence and potential risk factors responsible for kidney disease in Chinese PLWH should be conducted in the future.

Conclusion

In conclusion, the prevalence of kidney disease in HIV-infected patients in China is high. It is very important to monitor renal function and comprehensively manage the various risk factors in these people. Especially, there is an urgent need to study antiretroviral drugs with no or less nephrotoxicity and

with the ability to prevent the virus from depositing in the kidney to protect renal function of HIV-infected patients.

Abbreviations

HIV: human immunodeficiency virus; PLWH: people living with HIV; AIDS: Acquired Immune Deficiency Syndrome; ART: antiretroviral treatment; eGFR: estimated glomerular filtration rate; TDF: Tenofovir disoproxil fumarate; 3TC: Lamivudine; EFV: Efavirenz; HBV: hepatitis B virus; HCV: hepatitis C virus; Hb: hemoglobin; Alb: albumin; UA: uric acid; Hcy: homocysteine; PCT: procalcitonin; CRP: C reactive protein; TG: triglyceride; CHOL: total cholesterol; HDLC: high density lipoprotein cholesterol; LDLC: low density lipoprotein cholesterol; BMI: Body-mass index; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; CKD: chronic kidney disease; Scr: serum creatinine; SPSS: Statistical Package for Social Sciences; SD: standard deviation; IQR: interquartile range; CI: confidence interval; OR: odds ratio.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Beijing Ditan Hospital, Capital Medical University. The approval numbers is Jdlkz 2019-056-02.

Consent for publication

Not applicable.

Availability of data and materials

The data are available from the corresponding author with reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Naxin Zhao did the literature search, conceived and designed the study, and also drafted the first draft of the manuscript; Zhili Zeng participated in data collection; Hongyuan Liang, Fang Wang, Jiang Xiao, and

Di Yang managed patients and contributed to data collection; Meiling Chen participated in designation of the study and did the analyses; Guiju Gao conceived the study, revised and approved the manuscript. Pan Xiang supported the manuscript.

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Figures

Figure 1

Study flow chart detailing all the inclusion and exclusion of patients

eGFR: estimated glomerular filtration rate.