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Biomarkers and risk factors for sepsis in stage 5 chronic kidney disease: a retrospective case–control study

Lijuan Jiang[1] · Xiaonan Shao[2] · Wei Xing[3] · Yanbei Sun[4]

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Abstract

Purpose To assess the predictive value of procalcitonin (PCT) in the risk of sepsis in patients with stage 5 chronic kidney disease (CKD).

Methods A total of 373 inpatients with stage 5 CKD were retrospectively analyzed. The patients were divided into non-infection group, local infection group, and sepsis group. The clinical characteristics and inflammatory parameters including PCT, C-reactive protein (CRP), white blood cell count (WBC), and neutrophil percentage (NEU%) were compared and the receiver operating characteristic (ROC) curves to predict sepsis were plotted. Related risk factors of sepsis were analyzed by logistic regression analysis.

Results (1) The hemodialysis ratio of sepsis group was the highest at 92.3%. PCT, CRP, and NEU% were significantly different among the three subgroups ($P < 0.05$ for all). Total cholesterol and low density lipoprotein (LDL) levels in sepsis group were significantly lower than that in local infection group ($P < 0.05$ for both). (2) CRP and WBC were unable to predict sepsis ($P > 0.05$ for all), while PCT and NEU% could predict sepsis with areas under the curve (AUC) of 0.838 and 0.691, respectively ($P < 0.05$ for all). (3) Multivariate logistic regression analysis showed that PCT > 1.650 ng/mL was a risk factor ($OR = 6.926$, $P = 0.002$) while LDL was probably a protective factor ($OR = 0.336$, $P = 0.040$) of sepsis in patients with stage 5 CKD.

Conclusions At stage 5 CKD, the predictive value of PCT for sepsis is best among inflammatory markers, and PCT and LDL levels are independent factors of sepsis.

Keywords Chronic kidney disease · Procalcitonin · Low density lipoprotein · Sepsis · Risk factors

Lijuan Jiang and Xiaonan Shao are co-first authors.

✉ Yanbei Sun
sunyb-1985@163.com

Lijuan Jiang
czyyjlj@126.com

Xiaonan Shao
scorey@sina.com

Wei Xing
suzhxingwei@suda.edu.cn

[1] Department of Clinical Laboratory, The Third Affiliated Hospital of Soochow University, Changzhou 213003, China

[2] Department of Nuclear Medicine, The Third Affiliated Hospital of Soochow University, Changzhou 213003, China

[3] Department of Radiology, The Third Affiliated Hospital of Soochow University, Changzhou 213003, China

[4] Department of Nephrology, The Third Affiliated Hospital of Soochow University, Changzhou 213003, China

Abbreviations

CKD	Chronic kidney disease
PCT	Procalcitonin
CRP	C-reactive protein
WBC	White blood cell count
NEU%	Neutrophil percentage
ALAT	Alanine aminotransferase
ASAT	Aspartate aminotransferase
ROC	Receiver operating characteristic
AUC	Areas under the curve
ESRD	End-stage renal diseases
RRT	Renal replacement therapy
SIRS	Systemic inflammatory response syndrome
GFR	Glomerular filtration rate
eGFR	Estimated glomerular filtration rate
SCr	Serum creatinine
BUN	Blood urea nitrogen
TCHO	Total cholesterol
TG	Triglyceride

LDL	High density lipoprotein
HDL	Low density lipoprotein
PD	Peritoneal dialysis
HD	Hemodialysis
CAD	Coronary atherosclerotic disease

Introduction

As a public health problem, the high incidence and prevalence of CKD and its derived poor prognosis have led to high cost of medical and health maintenance [1, 2]. Sepsis is also a major challenge to clinicians and researchers and a global burden to healthcare systems and society for reasons of its high incidence and clinical complexity [3]. Due to functional decline in immune system [4], CKD patients are at a higher risk of serious infection [5]. Patients with end-stage renal disease (ESRD) have an increased risk of death compared with the general population. Infection is an important cause of death in ESRD patients. The US data also showed that sepsis was the second most common cause of death in ESRD patients [6, 7].

It is difficult to distinguish the infectious and non-infectious causes of systemic inflammatory response among CKD patients with simple consideration from clinical data [8], as a result of chronic kidney disease and systemic inflammatory status both increase the risk of sepsis [7, 9]. Procalcitonin (PCT) has now been considered as a precursory and diagnostic biomarker for infection, including sepsis, since 1993 [10]. Recent studies have found that raised PCT levels can be detected in the plasma of both infected and non-infected ESRD patients, including those who have not yet received renal replacement therapy, those who received intermittent peritoneal dialysis or hemodialysis, and those who were on maintaining renal replacement therapy (RRT) [11–15].

Previous studies of PCT in patients with renal insufficiency or uremia are still inconsistent, and several problems remain unresolved. First, to what extent elevated PCT concentration could reflect the decline in renal scavenging and the effect of micro-inflammatory state of uremia in uninfected CKD, including ESRD, patients [16–19]. Second, in the prediction of severe infection of patients with renal insufficiency or ESRD, is there any advantage of elevated PCT in differential diagnosis among inflammatory biomarkers including CRP etc. [11, 13]. However, so far, there are few studies on PCT in end-stage kidney disease and dialysis patients with relatively small available sample size or lack of representativeness [11, 20–24]. Further, little is known about the role of PCT in predicting sepsis in ESRD or dialysis patients. Therefore, our study is aimed to assess the predictive value of PCT in the risk of sepsis in patients with stage 5 CKD.

Materials and methods

General information

The study is a retrospective analysis of 471 inpatients with stage 5 CKD from January 2014 to March 2017 in our Department of Nephrology and has been approved by the Ethics Committee of the institution. CKD was defined by renal damage (abnormalities in pathological examination or had renal damage indicators, such as abnormal blood or urine compositions or imaging presentations) or an estimated glomerular filtration rate (GFR) < 60 mL/min/1.73 m^2 stable for more than 3 months. CKD was divided into 5 stages based on GFR. For patients that were not treated with dialysis, their estimated glomerular filtration rate (eGFR) was calculated using CKD-EPI formula and their CKD stage was performed based on the K/DOQI guidelines [25, 26]. Diagnosis of sepsis is based on international guidelines for management of severe sepsis and septic shock in 2012 [27]. Liver disfunction was defined as either alanine aminotransferase (ALAT) or aspartate aminotransferase (ASAT) positive. Patients were excluded if they had major surgery, severe cardiogenic shock or hypovolemic shock, acute pancreatitis (3 cases), nosocomial infection (20 cases), incomplete medical records (1 case), and received antibiotics within 1 week before admission (68 cases). At last, 373 patients were included in this study, including 231 males and 142 females. They were 61 ± 16 years old, ranging from 20 to 93, and classified into uninfected, locally infected, and sepsis subgroups.

Observation indicators

Patients' demographic data were recorded as follows: age at admission, gender, history of diabetes, hypertension, coronary artery disease, stroke, infection sites, and renal replacement therapy, vital signs at admission (body temperature, heart rate and respiratory rate), inflammatory indexes, including WBC (4–10 × 10^9/L), NEU% (40–75%), PCT, and CRP. Blood normal examination was conducted using Sysmex XN9000 (Hyogo, Japan). PCT was measured using Roche cobas8000 (Indianapolis, IN, USA) with reference ranging from 0.021 to 0.500 ng/mL. CRP with reference ranging from 0 to 10.0 mg/L and other biochemical indexes including ALAT (< 50U/L), ASAT (< 40U/L), serum creatinine (SCr, μmol/L), blood urea nitrogen (BUN, mmol/L), total cholesterol (TCHO, mmol/L), triglyceride (TG, mmol/L), high density lipoprotein (HDL, mmol/L), and low density lipoprotein (LDL, mmol/L) were measured using BECKMAN COULTER AU5800 (Brea, CA, USA). Blood gas analysis was conducted using

Roche cobas123 (Indianapolis, IN, USA) including blood carbon dioxide partial pressure ($PaCO_2$, mmHg). Blood cultures were measured using BD BACTEC FX (Sparks, MD, USA). The positive or negative cultures (blood culture, catheter tip culture, respiratory culture, urine culture, and other body fluid culture) were paired with the highest PCT before or 48 h after collection of the cultures. Blood samples were extracted before the use of antibiotics. PCT of all patients with CKD stage 5 was collected before they underwent peritoneal dialysis (PD) and hemodialysis (HD).

Statistical analysis

All data were analyzed using SPSS 13.0 statistical software. Measurement data with normal distribution were expressed as $\bar{x} \pm s$. Measurement data with non-normal distribution were expressed as median P50 (P25, P75). Count data were expressed in number or percentage. Two groups of data with normal distribution were compared using *t* test. Two groups of data with non-normal distribution were compared using one-way ANOVA. Two groups of data with non-normal distribution were compared using Mann–Whitney *U* test. Multi-group data were compared using Kruskal–Wallis *H* test. Rates were compared using χ^2 test. The ROC curves and the AUC were used to compare the diagnostic efficacy of different indexes. Correlation between data with non-normal distribution or between rates was analyzed using Spearman correlation analysis. Logistic regression analysis was applied to perform the multivariate analysis and calculate the odds ratio (OR) and 95% confidence interval (CI). $P < 0.05$ was considered statistically significant.

Results

Clinical characteristics and laboratory indexes of patients at CKD stage 5 without infection, with local infection, and sepsis

Among the 373 cases, 40 cases were in the non-infection group (10.7%), 307 cases in the local infection group (82.3%), and 26 cases in the sepsis group (7.0%). According to the location of infection, there were 21 cases (5.6%) of infection occurring in the abdominal cavity and peritoneal dialysis channel, 16 cases (4.3%) in the vascular access, 249 cases (66.8%) in the respiratory tract, 23 cases (6.2%) in the urinary tract, 23 cases (6.2%) in the gastrointestinal tract, 12 cases (3.2%) in skin, and 5 cases (1.3%) in other parts of the body.

Table 1 shows the clinical characteristics and laboratory indexes of patients in CKD stage 5 without infection, with local infection, and with sepsis. There was no significant difference in age, gender, and prevalence of diabetes and coronary atherosclerotic disease (CAD) among the three subgroups ($P > 0.05$ for both). However, the prevalence of hypertension in the sepsis group was significantly higher than that in the local infection group and non-infection group ($P < 0.05$ for both). And the prevalence of stroke in the local infection group was significantly lower than that in the non-infection group ($P < 0.05$). There were 24 patients (6.4%) with chronic viral hepatitis (19 patients with hepatitis B, 5 patients with hepatitis C), 19 patients (5.1%) had liver disfunction, and there were no significant differences in the proportion of chronic viral hepatitis and liver disfunction between the three groups ($P > 0.05$ for both). There was no significant difference in CRP between the patients with or without hepatitis and those with or without liver disfunction ($P > 0.05$ for both).

Three hundred and three (81.2%) patients were treated with dialysis, and the prevalence of infection in hemodialysis patients was significantly higher than that in other dialysis modalities and patients without dialysis ($P < 0.001$). The HD ratio of sepsis patients in the three subgroups was the highest at 92.3%. The median dialysis vintage of all dialysis patients was 1.5 years (range 1–17 years), and there was no significant difference between the three groups ($P > 0.05$). There was no significant correlation between dialysis vintage and PCT and CRP ($r = 0.047$ and 0.045, $P = 0.421$ and 0.559). There was a slight negative correlation between dialysis vintage and WBC and NEU% ($r = -0.189$ and -0.154, $P = 0.001$ and 0.008).

PCT, CRP, and NEU% were significantly different among the three subgroups ($P < 0.05$ for all). The increase of PCT level showed a downward trend in sepsis, local infection, and no infection, and there was a significant difference among the three groups ($P < 0.001$ for all). CRP in patients with sepsis and local infection was significantly higher than those in non-infection patients ($P < 0.05$ for all). There was no significant difference in CRP between patients with sepsis and those with local infection ($P > 0.05$). NEU% of sepsis patients were significantly higher than that of local infection patients and non-infection patients ($P < 0.05$ for all), but there was no significant difference between local infection patients and non-infection patients ($P > 0.05$).

Further Spearman correlation analysis showed a slight correlation between PCT and CRP and the degree of infection ($r = 0.365$ and $P < 0.001$ vs $r = 0.299$ and $P < 0.001$, respectively), whereas WBC and NEU% were weakly related to the degree of infection ($r = 0.110$ and $P = 0.036$ vs $r = 0.174$ and $P = 0.001$, respectively).

TCHO and LDL levels in sepsis group were significantly lower than that in the local infection group ($P < 0.05$ for both).

Table 1 Clinical characteristics and laboratory indexes of patients at stage 5 CKD without infection, with local infection, and sepsis

Characteristics	Non-infection group ($n=40$)	Local infection group ($n=307$)	Sepsis group ($n=26$)	$Z/\chi^2/F$	P
Age (years)	62 ± 18	61 ± 16	62 ± 15	0.118	0.889
Male (%)	28 (70.0)	184 (59.9)	19 (73.1)	2.993	0.224
Comorbidities					
DM (%)	9 (22.5)	107 (34.9)	11 (42.3)	3.400	0.183
HPT (%)	5 (12.5)	47 (15.3)	8 (30.8)#,*	3.999	0.135
CAD (%)	5 (12.5)	20 (6.5)	2 (7.7)	1.631	0.442
Stroke (%)	6 (15.0)	15 (4.9)*	3 (11.5)	5.879	0.053
Chronic viral hepatitis (%)	2 (5.0)	21 (6.8)	1 (3.8)	0.144	1.000
Liver disfunction (%)	3 (7.7)	24 (8.1)	5 (19.2)	3.514	0.148
Dialysis modalities					
Without dialysis (%)	14 (35.0)	56 (18.2)	0 (0.0)	30.441	< 0.001
HD (%)	16 (40.0)	192 (62.5)*	24 (92.3)#,*		
PD (%)	6 (15.0)	54 (17.6)	2 (7.7)		
HD and PD (%)	4 (10.0)	5 (1.6)	0 (0.0)		
Dialysis vintage (years)	2.0 (1.0, 5.5)	1.0 (1.0, 5.0)	1.0 (1.0, 3.0)	1.967	0.374
Laboratory indexes					
PCT (ng/mL)	0.313 (0.164, 0.571)	0.652 (0.317, 1.970)*	6.290 (1.745, 32.653)#,*	51.653	< 0.001
CRP (mg/L)	6.8 (4.0, 8.0)	27.0 (7.7, 75.0)*	46.1 (9.0, 171.0)*	20.871	< 0.001
WBC ($\times 10^9$/L)	6.39 (4.92, 10.62)	7.78 (6.02, 9.92)	8.99 (5.40, 14.82)	4.410	0.110
NEU% (%)	75.2 (66.2, 85.1)	77.6 (71.7, 85.2)	85.2 (78.2, 91.0)#,*	12.869	0.002
Albumin (g/L)	32.9 (27.8, 36.2)	30.4 (26.0, 33.8)	28.9 (25.4, 33.7)	3.810	0.149
BUN (mmol/L)	18.1 (14.1, 24.9)	19.6 (14.3, 25.9)	18.8 (15.3, 29.1)	0.755	0.686
SCr (μmol/L)	573 (379, 764)	648 (465, 851)	643 (456, 788)	3.176	0.204
TCHO (mmol/L)	3.48 (2.37, 4.32)	3.82 (3.19, 4.67)*	3.20 (2.66, 3.58)#	11.780	0.003
TG (mmol/L)	1.6 (1.1, 2.1)	1.5 (1.0, 2.2)	1.6 (1.3, 2.5)	0.772	0.680
HDL (mmol/L)	0.80 (0.60, 1.00)	0.92 (0.72, 1.13)*	0.78 (0.64, 1.14)	5.826	0.054
LDL (mmol/L)	1.56 (1.22, 2.16)	1.87 (1.41, 2.45)	1.33 (1.15, 1.75)#	12.745	0.002

DM diabetes mellitus, *HPT* hypertension, *CAD* coronary atherosclerotic heart disease, *HD* hemodialysis, *PD* peritoneal dialysis, *PCT* procalcitonin, *CRP* C-reactive protein, *WBC* white blood cell count, *NEU%* neutrophil percentage, *SCr* serum creatinine, *BUN* blood urea nitrogen, *TCHO* total cholesterol, *TG* triglyceride, *HDL* high density lipoprotein, *LDL* low density lipoprotein

*Significant difference compared with non-infection group

#Significant difference compared with local infection group

ROC curves of inflammatory indexes for sepsis in patients with stage 5 CKD

Figure 1 showed the ROC curve for predicting sepsis in patients with stage 5 CKD using PCT and NEU%. CRP and WBC were unable to predict sepsis of patients in CKD stage 5 ($P > 0.05$ for all). The AUC of PCT and NEU% for predicting sepsis were 0.838 and 0.691 at 95% CI of 0.797–0.874 and 0.640–0.738, respectively ($P < 0.05$ for all), as shown in Fig. 1. The sensitivity and specificity of PCT for predicting sepsis were 80.8% and 75.2%, respectively, at the optimum cutoff of 1.650 ng/mL, and those of NEU% for predicting sepsis were 76.9% and 55.5%, respectively, at the optimum cutoff of 78.8%.

Logistic regression analysis of sepsis in patients with stage 5 CKD

Univariate and multivariate logistic regression analyses were performed using sepsis as dependent variables and HD, PCT (> 1.650 ng/mL), NEU% (> 78.8%), TCHO, and LDL as independent variables. The results showed that PCT > 1.650 ng/mL was an independent risk factor ($OR = 6.926$, $P = 0.002$) while LDL level was an independent protective factor ($OR = 0.336$, $P = 0.040$) of sepsis in patients with stage 5 CKD (see Table 2).

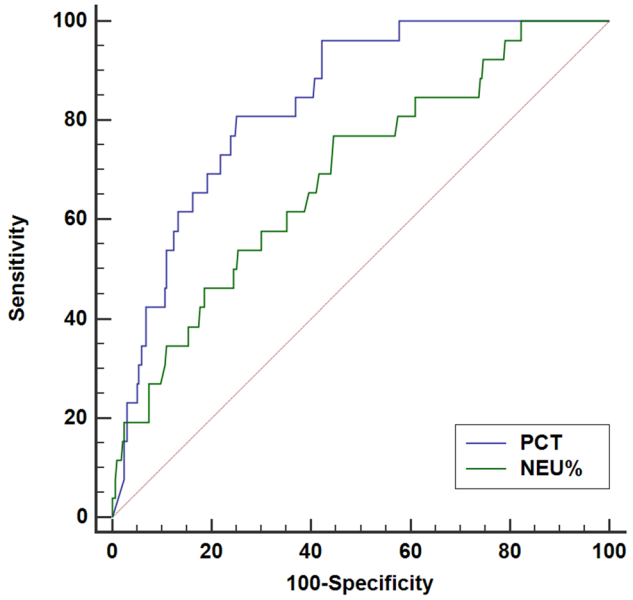

Fig. 1 ROC curve for predicting sepsis in patients with stage 5 CKD using PCT and NEU%. *PCT* procalcitonin, *NEU%* neutrophil percentage

Discussion

Sites of infection in patients at CKD stage 5

A community study reported by James et al. [28] noted that patients with low GFR had a higher risk of hospitalization and death. Infection increases the mortality in ESRD, and recently US data indicated that sepsis was the second leading cause of death [6, 7]. Because of the decreased immune function in ESRD population, increased hospitalization and mortality from infection could be driven by increased severity of infection, that is to say, once an infection occurs, the course of the associated illness is more severe or more frequent, thus ESRD may be more likely to cause an increase in the incidence of infections or sepsis. Our study showed that in patients with stage 5 CKD, sepsis accounted for 7.8% (26/333) of the overall infection. Thus, sepsis continues to be a common complication, and its important role in uremic patients should be fully assessed. We also found that the respiratory tract was the most common infection site, accounting for 66.8% in patients at CKD stage 5. In addition, there was a significant proportion of PD- and HD-related infections (5.6% and 4.3%, respectively) in patients at CKD stage 5. Previous studies found that PD patients are prone to PD-related peritonitis and tunnel infection [29–31], while HD patients are prone to tunnel infections, bloodstream infections, and catheter-related infection [28, 32]. Maintenance hemodialysis patients with chronic viral hepatitis and even cirrhosis represent a special patient population, and naturally, some studies on non-invasive detection of liver fibrosis have been derived [33, 34]. In our study, there was no significant difference in the proportion of chronic viral hepatitis and abnormal liver function among ESRD patients with different degrees of infection and non-infection.

Dialysis modalities and hypertension

The dialysis catheter and vascular access in ESRD patients may be a prominent risk factor for increased prevalence severity of infection. But it remains confused to what extent the results reflect the effect of renal replacement therapy, such as catheter and vascular access for dialysis, on infection incidence [5]. Our data suggested that hemodialysis modality was in a descent order for patients with sepsis, with local infection, and without infection; however, selection of dialysis modality was not found to be an independent risk factor for sepsis in our result.

In addition, our study showed that the proportion of hypertension in the sepsis group was significantly higher than that in the local infection group and non-infection group, but multivariate regression analysis did not show that hypertension was an independent risk factor for sepsis in uremic patients.

Table 2 Univariate and multivariate logistic regression analyses of sepsis in patients with stage 5 CKD

Factors	Univariate analysis *OR* (95% CI)	*P*	Multivariate analysis *OR* (95% CI)	*P*
HD	8.019 (1.865, 34.475)	0.005	4.269 (0.853, 21.377)	0.077
PCT (> 1.650 ng/mL)	12.747 (4.664, 34.832)	< 0.001	6.926 (2.039, 23.523)	0.002
NEU% (> 78.8%)	4.150 (1.626, 10.594)	0.003	1.255 (0.352, 4.478)	0.994
TCHO	0.456 (0.246, 0.844)	0.013	0.765 (0.210, 2.787)	0.888
LDL	0.239 (0.085, 0.671)	0.007	0.336 (0.119, 0.950)	0.040

HD hemodialysis, *PCT* procalcitonin, *NEU%* neutrophil percentage, *TCHO* total cholesterol, *LDL* low density lipoprotein, *OR* odds ratio, *CI* confidence interval

Predictive value of PCT for sepsis of patients at CKD stage 5

Infections account for a vast morbidity and mortality in uremia. Not infrequently, inflammation and infection biomarkers tend to overlap, and inflammatory laboratory indexes may be misleading and add confusion to an appropriate interpretation of these results due to uremia itself [35]. Since 1993, serum PCT has been evaluated as one of several inflammatory parameters for ruling out bacterial infections, improving the diagnosis of sepsis, and more reliably and accurately reducing inappropriate antibiotic exposure than traditional detection methods including CRP or WBC in the general population [36–39]. Recent studies have found that PCT has advantages in the diagnosis of systemic bacterial infection in CKD patients [12, 14].

Meta-analysis of Lu et al. [40] suggested that the cutoff value of PCT in chronic renal failure and ESRD patients could be divided into two sections: high diagnostic cutoff value (0.79–2.00 ng/mL) and low diagnostic cutoff value (0.38–0.50 ng/mL). Herget-Rosenthal et al. [11] also pointed out that PCT was an accurate indicator of severe infection and sepsis in HD patients, with an optimal cutoff value of 1.5 ng/mL which is similar to our result (1.650 ng/mL).

PCT was not fully compared with other inflammation-related biomarkers, such as CRP, WBC, NEU%, etc., especially in ESRD patients. Our findings demonstrated that the PCT level was intensively associated with sepsis in uremic patients, and its concentration was found to be the most discriminatory laboratory index in the diagnosis of sepsis, the AUC of which (0.838) exceeded that of NEU% (0.691), whereas CRP and WBC did not show the diagnostic ability for sepsis.

Multivariate regression analysis also confirmed that elevated PCT level was an independent risk factor for sepsis in uremic patients. Therefore, we recognized PCT as an optimal marker for predicting sepsis in uremic patients compared to other inflammatory indexes, which is consistent with previous researches.

Although the diagnostic efficacy of CRP has been frequently compared with that of PCT, previous studies on the correlation of severity of infection to CRP or PCT rarely involved patients with renal function impairment. Some studies showed that CRP level did not increase significantly with the development of the disease. Contrary to CRP, PCT level significantly increased in patients with severe organ dysfunction, sepsis or septic shock [37]. These differences may be due to that in the development of inflammation, the sources of CRP and PCT are different, and under severe infection conditions, CRP level in patients with liver dysfunction may not further increase [41].

Besides, NEU% are easily calculated and are immediately available from the full blood count in most hospitals, whereas PCT is not applicable in all hospitals because the necessary equipment is not available in some hospitals. The cost-effectiveness of PCT needs further study and discussion.

Possible protective effects of elevated LDL in sepsis in patients with stage 5 CKD

In the general population, previous studies have demonstrated that low cholesterol levels are a risk factor for sepsis [42], and others have suggested an association between low LDL and higher rates of community- and hospital-acquired sepsis [43, 44]. In our study, elevated LDL level was considered to be a protective factor of sepsis for disputes. The exact protection mechanism was unknown; however, LDL has been shown to facilitate bacterial toxin clearance in sepsis [45]. Therefore, one potential explanation for the increased sepsis risk with low LDL-C is the inability to clear bacterial toxins from the bloodstream [43]. On the other hand, dyslipidemia, including elevated LDL level and decreased HDL level, is a well-established traditional risk factor for CAD, while identifying and lowering LDL level in patients with CAD is one of the most commonly used medical instructions for cardiologists. Further, cardiovascular complication is the major cause of morbidity and mortality in ESRD patients [46]. Therefore, when ESRD encounters CAD and sepsis, the controlling of lipid metabolism disorder seems a double-edged sword for nephrologist, and the target range of LDL levels needs to be further explored.

This study also had several limitations. First, it was a retrospective study and may have certain bias in selection of uremia cases. Secondly, because the proportion of microbiologically confirmed infections in the study was not high. This study did not distinguish bacterial infections from non-bacterial infections, which may affect assessment of the diagnostic efficacy of PCT. Third, the sample size of the study population needs to be further expanded. Finally, we excluded cases received antibiotics within 1 week before admission, and the data of previous antibiotic use and previous interventions were not available.

Conclusions

In conclusion, PCT is proved to be the most reliable predictor of sepsis in CKD stage 5 patients. The best cutoff value of PCT is 1.650 ng/mL with the sensitivity of 80.8% and specificity of 75.2%. In addition, PCT is an independent risk factor of sepsis in patients with CKD stage 5, while LDL level is probably a protective factor.

Author contributions YS and XS conceived of the study, and drafted the manuscript. LJ carried out the Lab testing. XS participated in the design of the study and performed the statistical analysis.

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Data availability All data generated or analyzed during this study are included in this published article.

Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

Ethical approval The study has been approved by the Ethics Committee of Soochow University.

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