

Predictive value of procalcitonin in chronic allograft dysfunction in kidney transplant recipients

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Abstract. The present study was designed to determine the potential role of circulating procalcitonin (PCT) in predicting chronic allograft dysfunction (CAD) in kidney transplant recipients (KTRs). A total of 87 KTRs were retrospectively analyzed and divided into a CAD and a non-CAD (normal renal function) group. Clinical features and inflammatory markers were compared between the groups, including PCT, white blood cell count, C-reactive protein, neutrophil percentage (N%) and lipoprotein(a) [Lp(a)], and the receiver operating characteristic (ROC) curve for CAD prediction was plotted. Univariate and multivariate logistic regression analyses were used to analyze the relevant risk factors for CAD. The results indicated that i) the values of these indicators in the CAD group, including the male ratio, years after transplantation, PCT, N% and Lp(a), were significantly higher than those in the non-CAD group, while the body mass index, aspartate aminotransferase, high-density lipoprotein and low-density lipoprotein were significantly lower; ii) PCT and Lp(a) were able to predict CAD with an area under the ROC curve of 0.893 and 0.770, respectively; iii) multivariate logistic regression analysis of factors influencing CAD in KTRs suggested that elevated PCT was an independent risk factor. In KTRs, PCT was identified as a potential biomarker for predicting CAD.

Introduction

All over the world, ~40,000 organ transplants are performed per annum, among which kidney transplants are the most common procedure (1); however, most of the transplanted kidneys gradually develop functional failure within

10 years (2). In solid organ transplantation, chronic low-grade inflammation is thought to participate in chronic allograft dysfunction (CAD), the leading cause of late renal allograft dysfunction (3). Atherosclerosis, as one of the conditions associated with chronic low-grade inflammation, promotes the progression of CAD (4).

In 1993, the potential of circulating procalcitonin (PCT) as a biomarker for severe systemic inflammation, infection and sepsis was first suggested (5). Later studies have indicated that elevated PCT may be observed in patients with chronic kidney disease (CKD), regardless of the presence of any infection (6,7). A previous study identified a negative association between the baseline value of PCT and renal function in CKD patients (8). Low-grade inflammatory responses or a micro-inflammatory state in CKD patients are thought to cause an increase in pro-inflammatory metabolites and stimulation of the immune system, leading to increased release of inflammatory mediators and PCT entering the blood circulation. van Ree *et al* (4) reported that PCT may reflect chronic low-grade inflammation in a non-infected state that persists in the transplanted kidneys. In their study, the endpoint of the renal event was graft failure, return to dialysis, retransplantation or death, while mild to moderate-stage CAD was not among the items assessed. In addition, the levels of PCT after the acute phase of infection were not followed up.

Besides creatinine clearance and proteinuria, certain biomarkers are available to predict mild to moderate CAD of KTRs and clinicians are exploring novel non-invasive methods for entirely or partially replacing renal allograft biopsy for diagnosis of CAD. The aim of the present study was to assess the potential predictive value of circulating PCT concentrations for CAD in KTRs. Due to the high prevalence of infection in the KTRs who received long-term immunosuppressive agents compared with that in healthy subjects, patients with severe infections were therefore excluded. in the present study.

Materials and methods

General information. The present study was approved by the Ethics Committee of The Third Affiliated Hospital of Soochow University (Changzhou, China). A total of 92 KTRs from the Department of Nephrology, the Third Affiliated Hospital of Soochow University in Changzhou, P.R. China,

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were followed up after kidney transplant between March 2014 and September 2017, by collecting the data retrospectively. All medical records were anonymous and all patients provided written informed consent. The subjects that met the inclusion criteria were adults (>18 years of age) who had undergone kidney transplantation more than a year prior to their inclusion in this present study. Patients who had undergone major surgery in the past 5 years or had severe cardiogenic and/or hypovolemic shock (2 cases), severe infection (2 cases), graft loss (returning to dialysis, retransplantation or death, 0 cases) and incomplete medical records (1 case) were excluded. There was no clinical evidence of acute allograft rejection. Finally, a total of 87 KTRs aged 47±14 years (range, 23-77 years) were enrolled in the present study, including 66 males and 21 females. They were divided into a CAD group (n=42) and a non-CAD group (n=45). The KTRs were treated with triple immunosuppressive regimens, including a glucocorticoid, mycophenolic acid and calcineurin inhibitor.

Diagnosis. The definition of CAD was based on the Kidney Disease Improving Global Outcomes guidelines, specifically an estimated glomerular filtration rate (eGFR) <40 ml/min and/or proteinuria >500 mg/day (9). The Modification of Diet in Renal Disease Study formula was used to calculate the eGFR (10).

Observation indicators. The basic information of each patient was carefully recorded, including age, sex, weight, height, medical history (years after kidney transplantation, complications and infections), vital signs immediately after admission (temperature, heart rate and respiratory rate) and inflammatory markers, including white blood cells (WBC; reference range, 4-10×10⁹ cells/l), neutrophil percentage (N%; reference range, 40-75%), PCT and C-reactive protein (CRP; reference range, 0-10.0 mg/l). A Sysmex XN9000 (Hyogo) was used for normal blood tests. A Cobas8000 (Roche) was used to determine PCT with reference range of 0.021-0.500 ng/ml. An AU5800 (Beckman Coulter) was used to determine further biochemical indicators, including alanine aminotransferase (ALT; u/l), aspartate aminotransferase (AST; u/l), fasting blood glucose (FBG; mmol/l), creatinine (μmol/l), urea nitrogen (mmol/l), uric acid (μmol/l), triglyceride (TG; mmol/l), high-density lipoprotein (HDL; mmol/l), low-density lipoprotein (LDL; mmol/l) and lipoprotein(a) [Lp(a), mg/l]. Blood samples were measured within 24 h of admission and collected prior to the use of antibiotics.

Statistical analysis. SPSS 13.0 statistical software (SPSS, Inc.) was used for statistical analysis of all data. The Kolmogorov-Smirnov test was used to assess normality of distribution. Measurement data with a normal distribution are expressed as the mean ± standard deviation. The median (first and third quartile) was used to represent measurement data with a non-normal distribution. Count data are expressed as n (%). The independent samples t-test was used to compare data between two groups with a normal distribution. The Mann-Whitney U test was used to compare data between two groups with a non-normal distribution. The χ²-test was used for comparison of rates. The comparison between the diagnostic efficiencies of the different indicators was based on the receiver operating characteristic curve (ROC) analysis and

area under the curve (AUC). The sensitivity and specificity were calculated and the cut-off value was determined using the Youden index. Univariate and multivariate binary logistic regression analysis was used to calculate odds ratios (ORs) with 95% CI for the association of various parameters with the risk of CAD. P<0.05 was considered to indicate statistical significance.

Results

Clinical features of KTRs in the CAD and non-CAD group. The clinical features of KTRs in CAD and non-CAD group are listed in Table I. Compared with the non-CAD group, the CAD group had a higher ratio of male patients (P=0.010), a lower body mass index (BMI; P=0.041), a larger amount of years after transplantation (P<0.001), a higher serum concentration of PCT, N% and Lp(a) (P=0.001-0.004) and a lower serum concentration of AST, HDL and LDL (P=0.001-0.044). No differences between the two groups were identified in terms of age, frequency of local infection, location of infection, comorbidities, CRP, WBC, ALT, FBG and TG (all P>0.05).

Comparison of inflammatory markers between infected and non-infected patients. Among the 87 KTRs, 44 cases (49.4%) had an infection and 43 cases (50.6%) were without infection. No difference between the infected and non-infected patients was identified in terms of PCT, WBC and N% (all P>0.05), but the CRP in the infection group was significantly higher (P=0.045; Table II).

ROC curves of potential biomarkers for predicting CAD in KTRs. ROC curve analysis indicated that the CRP and WBC were not able to predict CAD in KTRs (P>0.05; the P-value is the probability that the observed sample AUC is found when, in fact, the true AUC is 0.5). The ability of PCT, N%, AST, HDL, LDL and Lp(a) to predict CAD in KTRs was demonstrated in Table III. Among these, PCT had the largest AUC (0.893), with a sensitivity of 85.7% and a specificity of 90.0% at the best cut-off value (0.086 ng/ml), followed by Lp(a), HDL and LDL; N% and AST had lower AUC (0.694 and 0.626, respectively) (Fig. 1).

Logistic regression analysis of CAD in patients after kidney transplantation. To determine the predictive value of PCT regarding CAD under exclusion of the interaction with other inflammatory indicators, logistic regression analysis was performed. The cohort of KTRs was stratified into two groups based on the serum PCT levels at the best cut-off value (0.086 ng/ml). CAD was regarded as the dependent variable, while gender, BMI, years after transplantation, PCT, N% AST, HDL, LDL and Lp(a) were taken as independent variables (Table IV). The results indicated that elevated PCT was a unique independent risk factor for CAD in KTRs (OR=40.500, 95%CI=3.093-530.293, P=0.005).

Discussion

Renal transplantation is considered a unique optimum therapy for patients with end-stage renal disease (ESRD). Despite the tremendous improvement in short-term renal allograft

Table I. Clinical characteristics of KTRs in the CAD and non-CAD groups.

Characteristic	Reference ranges	Non-CAD (n=45)	CAD (n=42)	t/ χ^2 /Z	P-value
Age (years)	-	44±16 ^a	50±10 ^a	1.888	0.063
Male gender	-	29 (64.4) ^b	37 (88.1) ^b	6.636	0.010
BMI (kg/m ²)	-	21.99±3.27 ^a	20.50±3.35 ^a	2.076	0.041
Time after transplantation (years)	-	6±5 ^a	11±5 ^a	3.847	<0.001
Local infection	-	22 (48.9) ^b	22 (52.4) ^b	0.106	0.745
Infection location					
Respiratory tract	-	10 (22.2) ^b	15 (35.7) ^b	1.931	0.165
Urinary tract	-	8 (17.8) ^b	4 (9.5) ^b	0.647	0.421
Gastrointestinal tract	-	4 (8.9) ^b	4 (9.5) ^b	0.000	0.786
Comorbidities					
Diabetes mellitus	-	2 (4.4) ^b	8 (19.0) ^b	3.232	0.072
Hypertension	-	5 (11.1) ^b	2 (4.8) ^b	0.481	0.488
Coronary heart disease	-	0 (0.0) ^b	0 (0.0) ^b	-	-
Stroke	-	0 (0.0) ^b	1 (2.4) ^b	-	0.483
Laboratory parameters					
PCT (ng/ml)	0.021-0.500	0.059 (0.041, 0.076) ^c	0.250 (0.163, 0.644) ^c	3.221	0.001
CRP (mg/l)	0-10.0	5.0 (3.9, 6.8) ^c	6.1 (4.4, 8.0) ^c	1.444	0.149
WBC (x10 ⁹ /l)	4-10	7.47 (5.81, 9.68) ^c	6.79 (5.33, 8.66) ^c	1.688	0.091
N%	40-75	66.2 (53.3, 74.1) ^c	74.8 (68.0, 80.9) ^c	3.054	0.002
ALT (u/l)	9-50	20 (13, 25) ^c	13 (7, 24) ^c	1.296	0.195
AST (u/l)	15-40	17 (15, 21) ^c	14 (12, 19) ^c	2.010	0.044
FBG (mmol/l)	3.90-6.10	4.51 (4.00, 5.08) ^c	5.01 (4.18, 5.82) ^c	1.939	0.052
TG (mmol/l)	0.70-2.02	1.48 (1.04, 2.16) ^c	1.30 (0.89, 2.30) ^c	0.080	0.936
HDL (mmol/l)	0.79-2.00	1.40 (1.05, 1.53) ^c	1.01 (0.78, 1.20) ^c	4.132	<0.001
LDL (mmol/l)	1.50-3.36	2.08 (1.72, 2.36) ^c	1.57 (1.18, 1.91) ^c	3.317	0.001
Lp(a) (mg/l)	0-300	48 (27, 103) ^c	121 (73, 239) ^c	2.861	0.004

^aValues are expressed as the mean ± standard deviation. ^bValues are expressed as the n (%). ^cValues are expressed as the median (first and third quartile). BMI, body mass index; PCT, procalcitonin; CRP, C-reactive protein; WBC, white blood cell count; N%, neutrophil percentage; ALT, alanine aminotransferase; AST, aspartate aminotransferase; FBG, fasting blood glucose; TG, triglycerides; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); CAD, chronic allograft dysfunction.

Table II. Comparison of inflammatory markers in the non-infection and local infection groups.

Characteristic	Non-infection (n=43)	Local infection (n=44)	Z	P-value
PCT (ng/ml)	0.071 (0.046, 0.162) ^a	0.187 (0.058, 0.419) ^a	1.123	0.261
CRP (mg/l)	4.9 (3.9, 6.6) ^a	6.1 (4.9, 8.8) ^a	2.008	0.045
WBC (x10 ⁹ /l)	7.04 (5.57, 9.58) ^a	7.18 (5.35, 9.11) ^a	0.228	0.820
N%	68.7 (58.1, 75.3) ^a	73.5 (59.1, 81.7) ^a	1.749	0.080

^aValues are expressed as the median (first and third quartile). PCT, procalcitonin; CRP, C-reactive protein; WBC, white blood cell count; N%, neutrophil percentage.

survival, long-term graft survival is limited, as most of KTRs fail within 10 years after transplantation. CAD is a complex process with multiple factors and is closely linked to progressive renal fibrosis and tubular atrophy.

CAD remains the leading cause of late graft failure (11). In the present study, the ratio of males in the CAD group was

higher, which means that males may be more likely to have poor renal transplant outcome than females. The reasons may include more frequent acute rejection due to a higher likelihood of human leukocyte antigen mismatch, no advantage in hormones and complex immunological processes, as well as worse compliance to immunosuppressants (12).

Table III. Predictive accuracy of various parameters for chronic allograft dysfunction in kidney transplant recipients determined by receiver operating characteristics curve analysis.

Parameter	AUC	P-value	Cut-off value	Sensitivity (%)	Specificity (%)
PCT (ng/ml)	0.893	<0.001	>0.086	85.7	90.0
N%	0.694	0.001	>67.1	80.0	54.5
AST (u/l)	0.626	0.045	≤15	57.5	71.1
HDL (mmol/l)	0.767	<0.001	≤1.27	89.5	58.1
LDL (mmol/l)	0.715	0.001	≤1.82	73.7	72.1
Lp(a) (mg/l)	0.770	<0.001	>83	72.7	70.6

AUC, area under the curve; PCT, procalcitonin; N%, neutrophil percentage; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein(a).

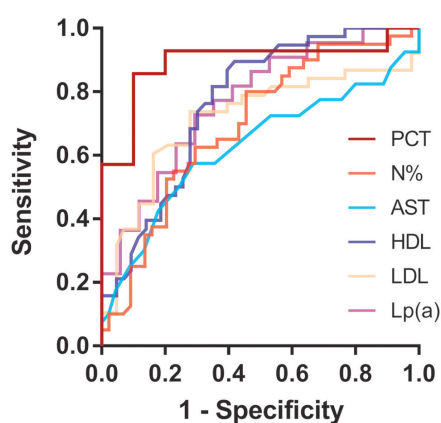


Figure 1. Receiver operating characteristic curves using PCT, HDL, LDL and Lp(a) to predict chronic allograft dysfunction of kidney transplant recipients. PCT exhibited the largest AUC compared with the other indexes. PCT, procalcitonin; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); AUC, area under the curve.

Obesity and increased BMI are considered to be accompanied by an elevated incidence of renal allograft insufficiency or CAD (13,14). However, the present results were not comparable with this, as the proportion of obese and overweight subjects in the CAD and the non-CAD group was very low. The lower BMI in the CAD vs. the non-CAD group of the present study may in part be explained by the distribution characteristics of the nutritional status of the subjects. Chronic inflammation, which is common in patients with uremia, is linked with malnutrition, resulting in a novel concept named malnutrition-inflammation complex syndrome, which was suggested to be independently associated with increased mortality risk and adverse transplant outcome (15).

The most noteworthy observation of the present study is the independent predictive value of serum PCT levels regarding the risk of progression to CAD in KTR patients. There are three reasonable explanations for this: i) The relatively high serum PCT level may reflect the activity of chronic low-grade inflammation in renal allograft rejection, which indirectly reflects the tendency of future progression to renal failure (16). Stimulated renal parenchymal cells may directly release PCT into the circulation in response to this sustained inflammatory response. Furthermore, indirectly, renal tissue

also releases cytokines into the bloodstream, which induces an increase in chronic low-grade production and induces other tissues, possibly including adipose tissue, to release PCT into the circulatory pool (17,18). ii) Proteinuria may be one of the mechanisms that link increased PCT concentration and CAD. van Ree *et al* (4) suggested that high levels of PCT, which may predict renal allograft failure, reflects the release of PCT by renal parenchymal cells into the circulation, and it is a feedback to the infiltration and activation of renal macrophages associated with proteinuria. iii) The same study indicated that PCT predicted non-proteinuric graft failure in KTRs, which may be due to the cascade of macrophage activity and interstitial inflammation being completely activated, even if the urinary protein level of renal tubular epithelial cells has not yet reached the upper limit of the reabsorption capacity, indicating PCT may be an earlier biomarker in the progression of CAD than proteinuria. Furthermore, the lower limit of the plasma PCT concentration for predicting the risk of CAD was 0.086 ng/ml, which is well below that of the presence of infection detected with the method of the present study. Therefore, an ultrasensitive assay is required to detect the PCT concentration.

Chronic rejection specifically refers to the progressive loss function of the transplanted kidney, the pathogenesis of which shares identical pathways with atherosclerosis (19). Lp(a), similar to other biomarkers of lipid metabolism, is a genetically-determined and forceful risk factor for atherosclerosis contributing to cardiovascular events (CVEs) (20). Increased Lp(a) levels, also considered a prototype candidate for the uremic toxin, are present in patients with CKD, including those with ESRD on dialysis (21-23). In the present study, among all lipid analysis indicators, Lp(a) was the most effective in predicting CAD of KTRs, as the AUC was the largest. Therefore, Lp(a) may be superior to HDL and LDL in predicting CAD. However, the mechanism of lipid metabolism affecting the progress of CAD remains to be fully elucidated. There are two hypothesized mechanisms of action. The former mechanism is that of the pathogenesis of endothelial dysfunction and macrovascular and small-vessel disease, which is composed of pro-inflammatory and pro-thrombotic properties of Lp(a), and in addition, oxidized phospholipids may lead to inflammatory reactions in cells and tissues. The strongest data supporting the latter hypothesis come from a temporal

Table IV. Univariate and multivariate logistic regression analysis of chronic allograft dysfunction in kidney transplant recipients.

Factor	Univariate		Multivariate	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age (years)	1.030 (0.998-1.063)	0.069		
Male gender	4.083 (1.338-12.459)	0.013	1.030 (0.060-17.788)	0.984
BMI (kg/m ²)	0.871 (0.761-0.997)	0.045	1.006 (0.661-1.531)	0.978
Years after transplantation	1.169 (1.069-1.280)	0.001	1.164 (0.900-1.505)	0.248
Diabetes mellitus	5.059 (1.008-25.396)	0.049	2.074 (0.383-11.226)	0.397
PCT (>0.086 ng/ml) ^a	54.000 (4.211-692.484)	0.002	40.500 (3.093-530.293)	0.005
WBC (x10 ⁹ /l)	0.863 (0.725-1.027)	0.096		
N% (>67.1) ^a	4.800 (1.809-12.737)	0.002	0.175 (0.002-16.428)	0.452
AST (≤15 u/l) ^a	3.330 (1.355-8.185)	0.009	2.205 (0.065-74.753)	0.660
HDL (≤1.27 mmol/l) ^a	11.806 (3.555-39.203)	<0.001	7.467 (0.201-276.716)	0.275
LDL (≤1.82 mmol/l) ^a	7.233 (2.708-19.322)	<0.001	7.594 (0.317-181.925)	0.211
LP(a) (>83 mg/l) ^a	6.400 (1.573-26.034)	0.010	9.364 (0.312-281.445)	0.198

^aValues in the brackets are the cutoff values of the parameters. BMI, body mass index; PCT, procalcitonin; WBC, white blood cell count; N%, neutrophil percentage; AST, aspartate aminotransferase; HDL, high-density lipoprotein; LDL, low-density lipoprotein; Lp(a), lipoprotein(a); OR, odds ratio.

evaluation of Lp(a) levels with a decline of >35% in patients after renal transplantation (22). The latter mechanism is the decreased renal scavenging capability of Lp(a) in patients with renal failure, which has been demonstrated by the distribution difference of the plasma Lp(a) concentration in renal arteries and veins and by the urine apolipoprotein A fragments (22). Such a negative correlation between Lp(a) levels and renal function, triggering a vicious circle, leads to CVEs even in patients with early renal impairment (22,24).

Based on a previous study, the predictive efficiency of PCT in local infection of CKD patients is not as good as that of traditional inflammatory biomarkers (e.g. CRP), yet it has a significant advantage in predicting sepsis (8). Similarly, in the present study, PCT was not able to identify local infection in renal transplant recipients. Thus, it may be speculated that in septic KTRs, PCT may principally participate in the systemic inflammatory response syndrome due to severe infection, while Lp(a) may be a more useful biomarker to predict CAD progression. Whether Lp(a) may be used as a valuable index for CAD in septic KTRs remains to be further explored.

Unlike previous studies, the present study did not exclude KTRs with focal infection, considering the high prevalence of infection due to the long-term use of immunosuppressive drugs. Of note, the levels of inflammatory markers, including PCT, N% and WBC, exhibited no statistically significant difference between the infection and non-infection subgroups, suggesting that these inflammatory markers are not able to predict focal infection in KTRs. Combined with the results of a recent study (8), as a by-conclusion of the present study, it may be suggested that PCT cannot predict local infection in CKD patients and KTRs with or without CAD.

The present study had a few limitations: i) It was limited by its retrospective nature; ii) given the small sample size, the conclusions require further confirmation by a larger-sample

survey; iii) the study was a single-center study with selection bias; iv) KTRs with severe infection, a common complication contributing to poor prognosis regarding graft survival, were not included in the study; v) the mechanism of lipid metabolism affecting the progress of CAD remains elusive.

In conclusion, PCT was proved to be a unique independent risk factor of CAD in KTRs. However, PCT, WBC and N% cannot predict local infection in KTRs except CRP. Therefore, even in KTRs with local infection, elevated PCT may still be a potential indicator for poor prognosis regarding renal graft survival.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

JY and YS conceived of the study, and drafted the manuscript. LJ and DX carried out the experiments. YS participated in the

design of the study and performed the statistical analysis. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of the Third Affiliated Hospital of Soochow University (Changzhou, China) and all patients signed informed consent forms.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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