

# Prediction Model for Early-Stage CKD Using the Naples Prognostic Score and Plasma Indoleamine 2,3-dioxygenase Activity

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**Purpose:** Changes in inflammation, immunity, and nutritional status can promote the development of chronic kidney disease (CKD), and the Naples prognostic score (NPS) reflects changes in these three general clinical parameters. Indoleamine 2,3-dioxygenase (IDO) can block the function of inflammatory cells and inhibit the production of inflammatory cytokines. We examined use of the NPS and IDO activity to predict early-stage CKD.

**Patients and Methods:** Clinical and demographic parameters and the NPS were recorded for 47 CKD patients and 30 healthy controls. A one-way ANOVA or the rank sum test was used to compare variables in the different groups. Spearman or Pearson correlation coefficients were calculated, and logistic regression was used to identify significant factors. Receiver operating characteristic (ROC) analysis was also performed.

**Results:** The NPS had a positive correlation with plasma IDO activity and IDO activity was lowest in controls, and increased with CKD stage. ROC analysis indicated that NPS had an area under the curve (AUC) of 0.779 when comparing controls with all CKD patients. A prediction model for CKD ( $-4.847 + [1.234 \times \text{NPS}] + [6.160 \times \text{plasma IDO activity}]$ ) demonstrated significant differences between controls and patients with early-stage CKD, and for patients with different stages of CKD. This model had AUC values of 0.885 (control vs CKD1–4), 0.876 (control vs CKD2), 0.818 (CKD2 vs CKD3), and 0.758 (CKD3 vs CKD4).

**Conclusion:** A prediction model based on the NPS and IDO provided good to excellent predictions of early-stage CKD.

**Keywords:** inflammation, immune, nutrition, score, metabolomic, kynurenine pathway

## Introduction

Chronic kidney disease (CKD) has a high prevalence worldwide and a prevalence of about 10.8% in China.<sup>1,2</sup> The number of cases has also increased during recent decades, and CKD now accounts for significant healthcare costs.<sup>3,4</sup> Patients with CKD experience a reduced quality of life and significant lifestyle limitations. The biomarkers commonly utilized for detecting CKD, such as serum creatinine (SCr) and cystatin C (CysC), are insufficiently sensitive and specific for early detection of disease. Because patients with early-stage CKD (CKD1–2) also lack obvious symptoms, diagnosis often occurs when patients have CKD3, a stage when treatment is much more challenging.

Changes in inflammation, immunity, and nutritional status can contribute to the onset and progression of CKD. Tryptophan, an essential amino acid, is metabolized through the kynurenine pathway by the rate-limiting enzymes Indoleamine 2,3-dioxygenase (IDO) and Tryptophan-2,3-dioxygenase (TDO), with over 95% of free tryptophan following this route. The main role of tryptophan in maintaining immune homeostasis and protective tolerance is predominantly through IDO.<sup>5,6</sup> In the liver, the initial step in tryptophan degradation is facilitated by TDO, which typically accounts for the majority of this conversion. The non-liver branch of the kynurenine pathway is regulated by two IDO enzymes (IDO1 and IDO2), whose function is minimal under normal circumstances but significantly increases in response to various stimuli, including inflammatory signals such as TGF- $\beta$ .<sup>7,8</sup> Overexpression of IDO leads to tryptophan depletion, which

can cause effector T cell incompetence and apoptosis.<sup>9,10</sup> High expression of IDO can also disrupt the function of inflammatory cells and reduce the levels of inflammatory cytokines.<sup>11,12</sup> Our previous research identified significantly increased levels of the plasma and urine levels of IDO in patients with early-stage CKD, and that these levels were also associated with inflammation due to CKD.<sup>13,14</sup> Therefore, measurement of IDO activity along with other indicators may allow the timely and accurate prediction of early CKD and CKD progression.

The Naples prognostic score (NPS) is commonly used to evaluate the inflammatory and nutritional status of patients, especially those with different cancers. This score is a function of the level of four blood markers (neutrophil-to-lymphocyte ratio [NLR], lymphocyte-to-monocyte ratio [LMR], serum albumin, and total cholesterol), and a high score reflects a systemic inflammation and poor immunological and nutritional status. Galizia et al first proposed the NPS in 2017 for the prognostic assessment of patients with colorectal cancer.<sup>15</sup> Because these four blood markers are easy to measure and the calculation is simple, subsequent researchers have used the NPS to assess the prognosis of patients with a variety of different tumors. The presence of systemic inflammation, immune status disorders, and poor nutritional status of CKD patients have long been puzzling for clinicians. Nonetheless, there is evidence that the NLR and LMR were significantly different between CKD patients and healthy people, and may be useful for prediction of CKD.<sup>16</sup> There is also evidence that CKD patients have aberrant levels of albumin and total cholesterol, reflecting a poor nutritional status.<sup>17–19</sup> Thus, a prediction model based on inflammation, immune status, and nutritional status may fully reflect the overall condition of patients with early-stage CKD.

In this study, we examined use of the NPS and IDO activity, clinical variables that are affected by systemic inflammation, immunity, and nutritional status, for the prediction of early-stage CKD and progression of CKD.

## Materials and Methods

A total of 47 patients and 30 controls were prospectively recruited from the First Affiliated Hospital of Soochow University (Suzhou, Jiangsu) from March to June 2018. We previously analyzed different clinical variables in this same population.<sup>13,14</sup> Subjects with any of the following characteristics were excluded: below 18-years-old, autoimmune-related nephritis, strict vegetarianism, severe arrhythmia or heart failure, cancer, participation in professional athletics, a solitary kidney, lactation, and pregnancy. All 47 patients had diagnoses of stage 1 to stage 4 CKD (CKD1–4) according to the Kidney Disease Improving Global Outcome guideline.<sup>20</sup> All patients had CKD1–4, as determined by the KIDGO guideline. All subjects were diagnosed with CKD for the first time and did not undergo any treatment before this diagnosis. The glomerular filtration rate was estimated using the Chronic Kidney Disease Epidemiology Collaboration equation.<sup>17</sup> The study was approved by the Ethics Committee of the First Affiliated Hospital of Soochow University (Ethics Research Association No. 079), and each individual provided written informed consent prior to participation. Our study complied with the Declaration of Helsinki.

## Laboratory Measurements

Laboratory measurements were determined by the OLYMPUS AU2700 automatic biochemical analyzer (Olympus, Japan) and the Beckman LH750 automatic blood analyzer (Beckman, U.S.A). IDO activity was determined as the ratio of kynurenine to tryptophan,<sup>21–24</sup> which were measured using liquid chromatography (Ultimate 3000, Thermo, USA) coupled with mass spectrometry (Q Exactive, Thermo, U.S.A). The NPS (range: 0 to 4) was calculated as the sum of the scores for four variables, in which an abnormal level of serum albumin (<40 g/L), total cholesterol ( $\leq 4.65$  mmol/L), NLR ( $> 2.96$ ), and LMR ( $\leq 4.44$ ) was assigned a value of 1 (Table 1).

**Table 1** NPS System

Points	Albumin (g/L)	Total Cholesterol (mmol/L)	NLR	LMR
0	$\geq 40$	$> 4.65$	$\leq 2.96$	$> 4.44$
1	$< 40$	$\leq 4.65$	$> 2.96$	$\leq 4.44$

**Abbreviations:** NPS, Naples prognosis score; NLR, neutrophil-to-lymphocyte ratio; LMR, lymphocyte-to-monocyte ratio.

## Statistical Analysis

SPSS version 22.0 was used for all statistical analyses. Data that had normal distributions were expressed as means  $\pm$  standard deviations (SDs), and data that had non-normal distributions were expressed as medians and interquartile ranges (IQRs). A one-way ANOVA, *t*-test, or the rank sum test was used to compare variables. Pearson or Spearman correlation analysis was used to calculate the correlations between pairs of variables. Binary logistic regression was used to determine the significance and independence of the relationship of various factors with CKD. To evaluate the accuracy in the prediction of CKD, receiver operating characteristic (ROC) curves were used. To identify the optimal cut-off point for the ROC curve, Youden's index was calculated. A *P* value below 0.05 (\*) was considered statistically significant.

## Results

### Clinical Characteristics of CKD Patients and Controls

We enrolled 30 controls and 47 patients with CKD1–4 (Table 2). We first measured the variance homogeneity and distribution normality of all the basic clinical variables; variables with homogeneous variances and normal distributions were analyzed using ANOVA, and other variables were analyzed using the rank sum test. The control group and the CKD1–4 group had significant differences in hemoglobin, SCr, blood urea nitrogen (BUN), serum albumin, NLR, LMR, plasma IDO activity, and urine IDO activity (all *P* < 0.05). It should be noted that a previous paper we published was with the same population and baseline data.<sup>10</sup>

### NPS in CKD Patients and Controls

We compared the mean NPS of the control group with different groups of CKD patients. The control group had a significantly lower NPS than the CKD1–4 group (Figure 1A) and a lower NPS than patients who had CKD1, CKD2, and CKD4 (Figure 1B).

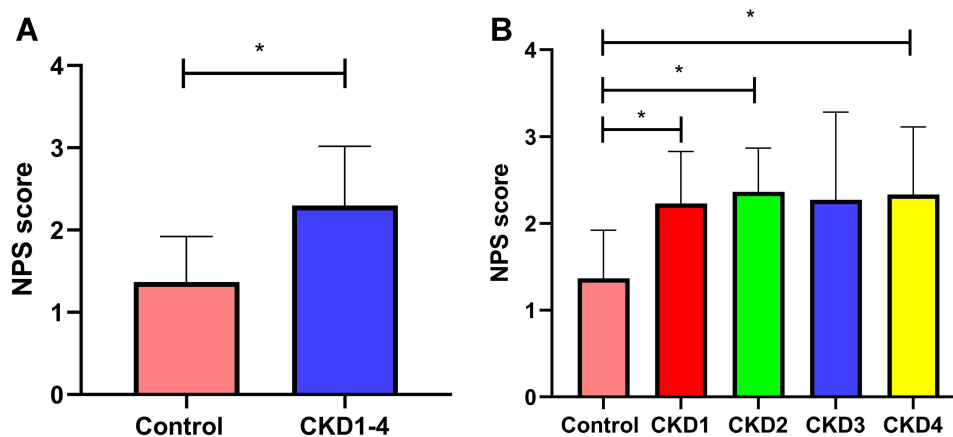
ROC analysis that used the NPS demonstrated the prediction of CKD1–4 had an area under the curve (AUC) of 0.779 (*P* < 0.05, Figure 2A). The AUC was 0.721 (*P* < 0.05) for prediction of CKD1 (Figure 2B) and was 0.820 (*P* < 0.05) for prediction of CKD2 (Figure 2C).

**Table 2** Clinical Characteristics of CKD Patients and Controls

Variable	Control	CKD1	CKD2	CKD3	CKD4	<i>P</i>
Gender, M/F	10/20	5/8	7/4	6/5	7/5	
Age, years	48 $\pm$ 12	47 $\pm$ 16	51 $\pm$ 21	56 $\pm$ 17	58 $\pm$ 14	0.232
Uric acid, $\mu$ mol/L	344.5 $\pm$ 91.0	379.8 $\pm$ 122.7	430.3 $\pm$ 59.8	431.2 $\pm$ 129.7	420.4 $\pm$ 138.4	0.060
Hemoglobin, g/L	140.0 $\pm$ 11.4	128.5 $\pm$ 17.7	126.6 $\pm$ 11.4	121.9 $\pm$ 12.9	111.3 $\pm$ 17.9	<0.05
Creatinine, $\mu$ mol/L	62.2 (53.4, 68.8)	58.1 (49.2, 63.3)	93.9 (77.1, 104.3)	134.0 (120.5, 152.0)	241.8 (212.0, 258.9)	<0.05
Blood urea nitrogen, mmol/L	4.7 (4.0, 5.3)	5.2 (3.3, 5.9)	6.3 (5.6, 7.5)	8.3 (7.7, 11.6)	12.8 (9.4, 15.1)	<0.05
Triglycerides, mmol/L	1.2 (0.9, 1.9)	1.5 (0.9, 2.3)	1.4 (0.9, 1.9)	1.7 (1.2, 2.0)	1.7 (1.2, 2.4)	0.403
BMI, kg/m <sup>2</sup>	23.7 (20.9, 25.2)	24.0 (22.1, 27.0)	23.0 (21.3, 24.4)	24.8 (22.9, 26.9)	24.5 (22.0, 25.6)	0.464
Albumin, g/L	47.7 (46.0, 48.6)	35.6 (28.7, 40.4)	39.6 (37.4, 42.5)	42.9 (38.9, 44.4)	41.4 (38.1, 42.8)	<0.05
Total cholesterol, mmol/L	4.5 (3.9, 5.2)	5.2 (4.1, 5.6)	4.7 (4.5, 5.5)	4.5 (4.2, 5.1)	4.5 (3.8, 5.2)	0.419
Blood glucose, mmol/L	4.9 (4.6, 5.2)	4.6 (4.5, 4.8)	4.6 (4.1, 4.9)	4.7 (4.1, 4.8)	4.6 (4.3, 5.0)	0.086
hs-CRP mg/L	0.1 (0.1, 0.2)	0.8 (0.5, 1.0)	2.3 (1.6, 3.6)	5.1 (3.8, 6.2)	5.9 (2.8, 7.0)	<0.05
NLR	1.7 (1.4, 2.0)	2.2 (1.7, 2.5)	2.3 (1.7, 2.5)	2.8 (1.5, 3.0)	2.2 (1.8, 2.8)	<0.05
LMR	5.0 (3.8, 6.6)	4.4 (3.7, 7.1)	3.6 (2.6, 4.1)	3.3 (2.5, 6.6)	3.2 (2.7, 4.6)	<0.05
Plasma IDO activity	0.5 $\pm$ 0.1	0.5 $\pm$ 0.1	0.6 $\pm$ 0.1	1.0 $\pm$ 0.2	1.3 $\pm$ 0.4	<0.05
Urine IDO activity	1.2 $\pm$ 0.6	1.0 $\pm$ 0.4	2.8 $\pm$ 4.6	3.7 $\pm$ 2.5	5.6 $\pm$ 2.7	<0.05
NPS	0.9 $\pm$ 0.6	1.6 $\pm$ 0.9	1.8 $\pm$ 0.6	1.9 $\pm$ 1.1	2.0 $\pm$ 0.9	<0.05

**Note:** Values are indicated as mean  $\pm$  SD or median.

**Abbreviations:** CKD, chronic kidney disease; BMI, body mass index; NLR, Neutrophil-to-Lymphocyte ratio; LMR, Lymphocyte-to-monocyte ratio; IDO, Indoleamine 2,3-dioxygenase; NPS, Naples Prognostic Score.



**Figure 1** NPS of controls and CKD1–4 patients (A) and patients with different stages of CKD (B). (A and B): Changes in CKD1–4 and each stage of CKD1–4. \* $P < 0.05$ . **Abbreviations:** NPS, Naples prognosis score; CKD, chronic kidney disease.

## Correlations of NPS Score with Clinical Indices

We then investigated the relationship between NPS and multiple clinical indices by analysis of data from all controls and all CKD patients (Figure 3). The results revealed that the NPS had significant positive correlations with plasma IDO activity ( $r = 0.46$ ,  $P < 0.05$ ), urine IDO activity ( $r = 0.41$ ,  $P < 0.05$ ), SCr ( $r = 0.43$ ,  $P < 0.05$ ), age ( $r = 0.32$ ,  $P < 0.05$ ), uric acid ( $r = 0.24$ ,  $P < 0.05$ ), and BUN ( $r = 0.43$ ,  $P < 0.05$ ), and a significant negative correlation with hemoglobin ( $r = -0.25$ ,  $P < 0.05$ ).

## IDO Activity in CKD Patients and Controls

We also found significantly higher plasma and urine IDO activities in the CKD1–4 group than in the control group (Figure 4A and C) and in the CKD2 group than in control group (Figure 4B and D). Furthermore, plasma and urine IDO activity increased progressively with CKD stage.

## Early-Stage CKD Prediction

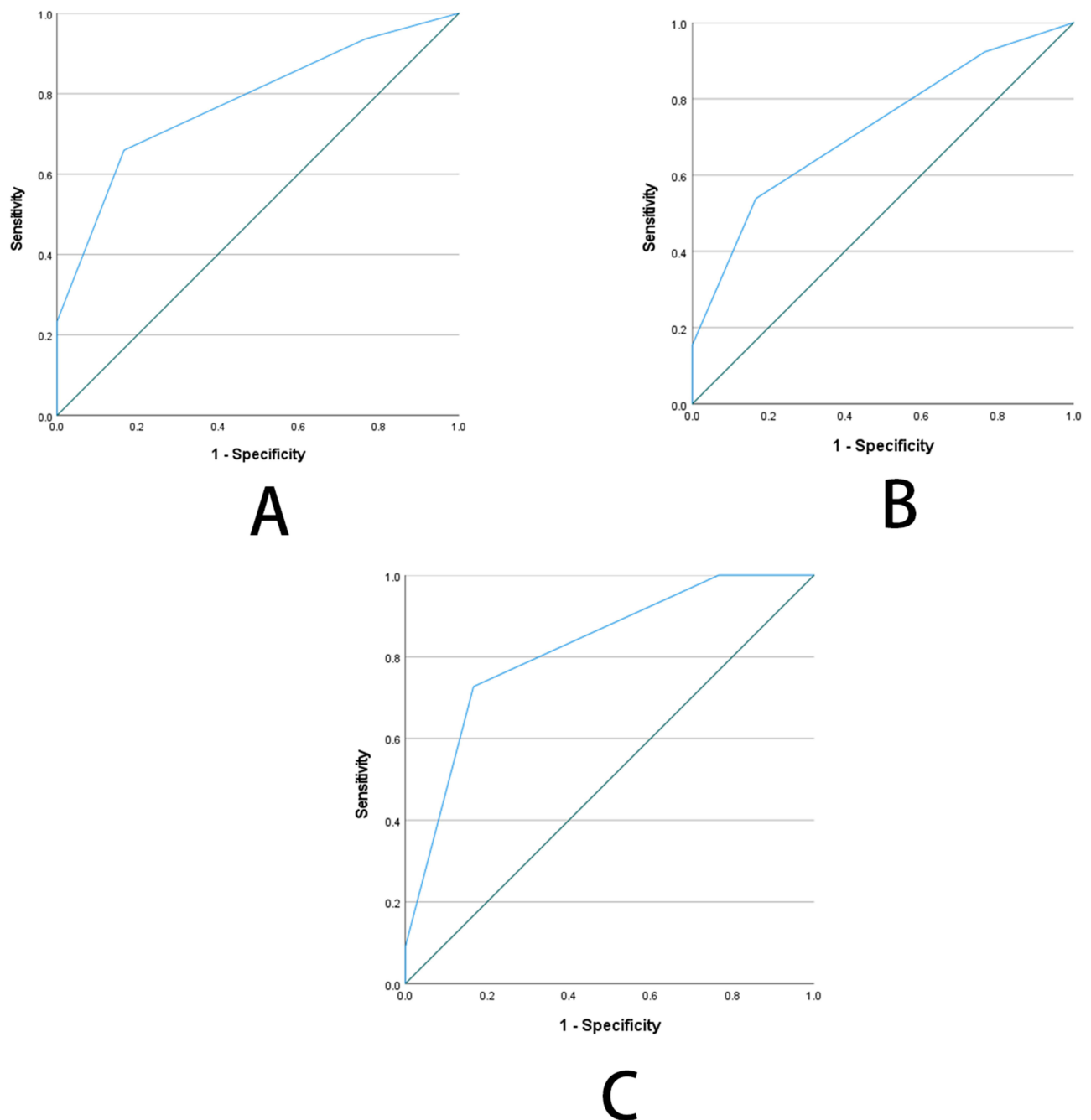
We conducted a ROC analysis to compare the predictive value of NPS, plasma IDO activity, urine IDO activity, and creatinine. In both the control group and CKD stage 1–4 patients, NPS, plasma IDO activity, urine IDO activity, and creatinine all showed predictive value (AUC= 0.776, 0.833, 0.742, 0.798,  $P < 0.05$ ). Among these, plasma IDO activity demonstrated the highest predictive value (Figure 5A). In the control group and CKD stage 1–2 patients, NPS and plasma IDO activity exhibited predictive value (AUC= 0.766, 0.683,  $P < 0.05$ ), while urine IDO and creatinine did not show any predictive value (Figure 5B).

## Inflammation Prediction of CKD Stage

We performed ROC analysis to determine the value of plasma IDO activity, urine IDO activity, NLR, LMR in predicting inflammation due to CKD (Figure 6). Plasma IDO activity showed a high predictive value, with an AUC of 0.833 (95% CI: 0.744–0.923,  $P < 0.05$ ), best cut-off value of 0.563, sensitivity of 69.6%, and specificity of 86.7%. Urine IDO activity had an AUC of 0.742 (95% CI: 0.633–0.851,  $P < 0.05$ ), best cut-off value of 0.413, sensitivity of 41.3%, and specificity of 100%. NLR had an AUC of 0.711 (95% CI: 0.593–0.829,  $P < 0.05$ ), best cut-off value of 0.432, sensitivity of 56.5%, and specificity of 86.7%. LMR had an AUC of 0.308 (95% CI: 0.189–0.427,  $P < 0.05$ ), best cut-off value of 0.030, sensitivity of 13.0%, and specificity of 90.0%.

## Prediction Model of CKD

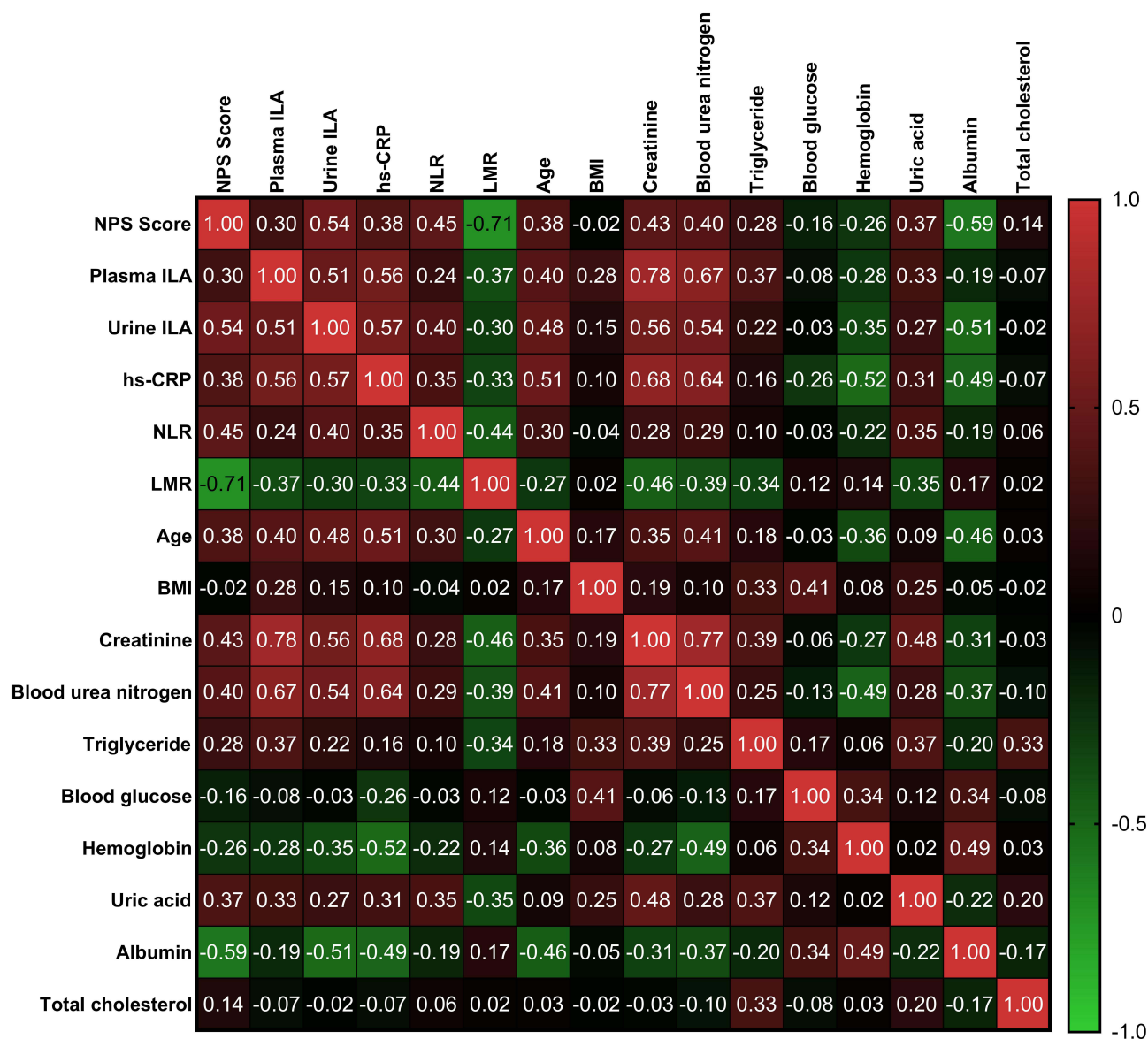
Analysis of the control group and CKD1–4 group demonstrated there were significant correlations of the NPS with plasma IDO activity, urine IDO activity, age, urea nitrogen, and uric acid. We therefore conducted logistic regression



**Figure 2** Receiver operating characteristic analysis for prediction of CKD1–4 (A), CKD1 (B) and CKD2 (C) based on the NPS of controls and CKD patients. **Abbreviations:** CKD, chronic kidney disease; NPS, Naples prognosis score.

analysis using these variables (Table 3). The results showed that the NPS (OR = 3.435,  $P < 0.05$ ) and plasma IDO activity (OR = 473.622,  $P < 0.05$ ) were significant and independent predictors of CKD1–4.

We then constructed a model for prediction of CKD using the results of this logistic regression model:  $-4.847 + (1.234 \times \text{NPS}) + (6.160 \times \text{plasma IDO activity})$ . Use of this model indicated there were significant differences between the control group and the CKD1–4 group (Figure 7A) and between the control group and the CKD1 group (Figure 7B). In addition, there was a gradual and significant upward trend from CKD1 to CKD4 (Figure 7B).

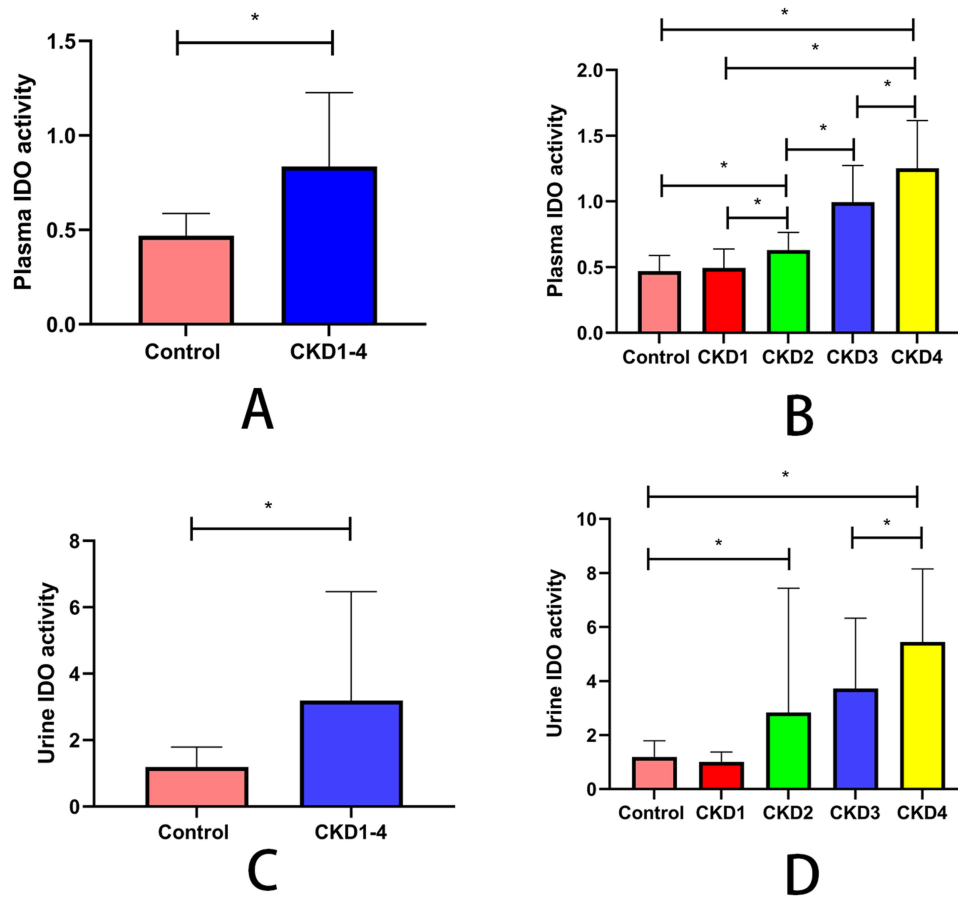


**Figure 3** Pair-wise correlations of NPS and other clinical indices in controls and CKD1–4 patients. **Abbreviations:** NPS, Naples prognosis score; IDO, indoleamine 2,3-dioxygenase; BMI, Body Mass Index.

ROC analyses using the same prediction model showed the AUC was 0.885 ( $P < 0.05$ ) for prediction of CKD1–4 vs control (Figure 8A), 0.715 ( $P < 0.05$ ) for prediction of CKD1 vs control (Figure 8B), 0.818 ( $P < 0.05$ ) for CKD2 vs CKD3 (Figure 8C), and 0.758 ( $P < 0.05$ ) for CKD3 vs CKD4 (Figure 8D).

## Discussion

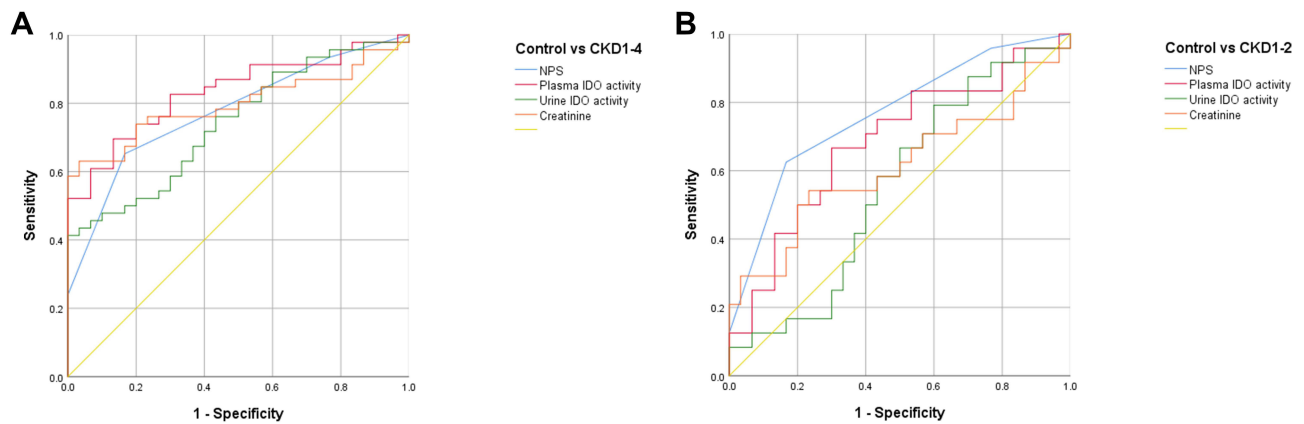
In this study, we examined the use of NPS and IDO activity to predict early-stage CKD and progression of CKD. We included IDO measurements because our previous work found a relationship between IDO and inflammation due to CKD.<sup>13,14</sup> To our knowledge, this is the first study to evaluate use of the NPS for prediction of CKD. A univariate logistic regression analysis showed that NPS was a significant predictor of CKD. We then included additional clinical parameters and performed multivariate logistic regression analysis. The results demonstrated that NPS and plasma IDO activity were significant and independent predictors of CKD. Therefore, we then used these results to develop a prediction model based the NPS and plasma IDO activity. The prediction model demonstrated statistically significant differences between the healthy control group the CKD1–4 group, and also showed good-to- excellent predictions of



**Figure 4** Plasma IDO activity (A and B) and urine IDO activity (C and D) in CKD patients and controls.

**Note:** \*P <0.05.

**Abbreviations:** CKD, chronic kidney disease; IDO, indoleamine 2,3-dioxygenase.

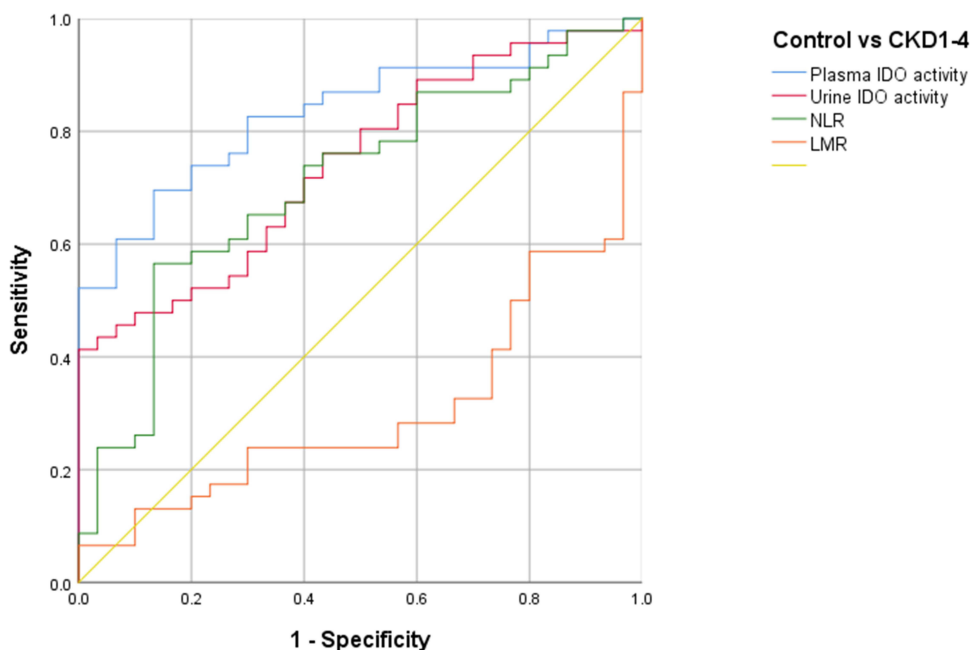


**Figure 5** Receiver operating characteristic analysis for early-stage CKD prediction.

**Notes:** (A) Prediction for CKD1-4, (B) Prediction for CKD1-2.

**Abbreviations:** CKD, chronic kidney disease; IDO, indoleamine 2,3-dioxygenase; NLR, Neutrophil-to-Lymphocyte ratio; LMR, Lymphocyte-to-monocyte ratio.

early-stage CKD (CKD2) and progression of CKD. Although this study uses the same population and data as previous work,<sup>14</sup> including IDO activity, it still provides an interesting perspective. By incorporating the NPS system and IDO activity, which has not been utilized by CKD before, it aims to comprehensively explore the evaluation system for CKD patients based on nutrition, immunity, and inflammation.



**Figure 6** Receiver operating characteristic analysis for prediction inflammation of CKD.

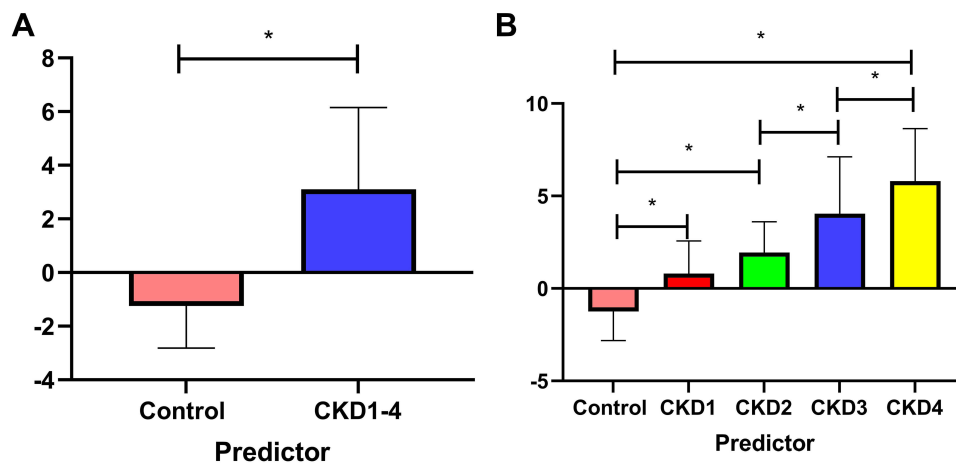
**Abbreviations:** CKD, chronic kidney disease; IDO, indoleamine 2,3-dioxygenase; NLR, Neutrophil-to-Lymphocyte ratio; LMR, Lymphocyte-to-monocyte ratio.

The NPS is based on four markers of inflammation and nutritional status: NLR, LMR, serum albumin, and total cholesterol. Researchers and clinicians primarily use this scale to assess the prognosis of patients with different types of cancer. We used the NPS for evaluation of CKD because these patients also experience increased systemic inflammation and deficient nutritional status. Previous research found that an elevated NLR was associated with an increased risk of end-stage kidney disease.<sup>25,26</sup> Yoshitomi et al discovered a correlation between a high NLR and negative renal outcomes, suggesting that NLR had potential as a prognostic marker for patients with renal disease.<sup>27</sup> There is also evidence that the NLR could serve as a supplementary marker for predicting the onset of uremic symptoms and the need for hemodialysis in patients with CKD5.<sup>28</sup> Chen et al reported that an elevated NLR was associated with longer hospital stay and more dialysis sessions.<sup>29</sup> Other studies of hemodialysis patients concluded that the NLR was a predictor of mortality and cardiovascular events in hemodialysis patients.<sup>30,31</sup> Our results revealed that the control group and CKD1–4 group had significant differences in the NLR and LMR. These markers are commonly utilized to predict inflammation in various diseases, including CKD, and alterations in inflammatory and immune status are crucial factors that affect the progression of CKD. However, targeted treatments of the complex changes that occur during systemic inflammation and altered immunity on CKD have not yielded satisfactory clinical outcomes. Therefore, we suggest that further mechanistic investigations based on our results may be beneficial in identification of new treatments for CKD.

Several previous studies reported that CKD patients had low levels of serum albumin and total cholesterol levels, and red blood cells with a decreased lifespan.<sup>32–34</sup> Similarly, a cohort study of Chinese patients found that incident CKD was associated with a low blood level of total cholesterol, although a Mendelian randomization analysis showed that CKD only had a causal relationship with the level of triglycerides.<sup>35</sup> Konje et al discovered a significant difference in the total

**Table 3** Ordinal Logistic Regression Analysis of Independent Predictors on CKD

Variable	Exp(B)	B	P
NPS score	3.435	1.234	<0.05
Plasma IDO activity	473.622	6.160	<0.05
Constant	0.008	-4.847	<0.05



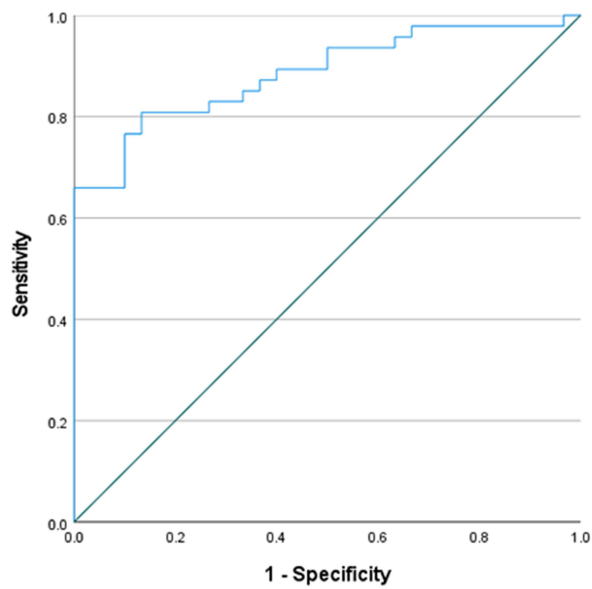
**Figure 7** Prediction of CKD1–4 (A) and different stages of CKD (B).

**Notes:** \* $P < 0.05$ . Prediction model:  $CKD = -4.847 + (1.234 \times NPS) + (6.160 \times \text{plasma IDO activity})$ .

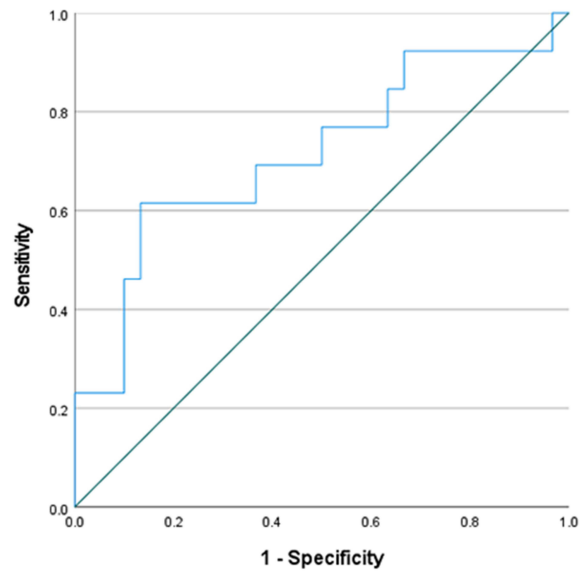
cholesterol level of patients who had CKD without cardiovascular disease and patients who had CKD with cardiovascular disease, and another study found that changes in lipid metabolism correlated with the extent of proteinuria.<sup>36,37</sup> We observed a significant difference in the level of serum albumin (a nutritional indicator) between the control group and the CKD1–4 group, most notably in patients with early-stage CKD. These findings emphasize the importance of monitoring the nutritional status of CKD patients so that clinicians can implement prompt interventions. It is likely that adequate attention to the nutritional needs of CKD patients will greatly improve prognosis. Importantly, our results demonstrated that the healthy control group had a significantly lower NPS than the CKD1–4 group, CKD1 group, and CKD2 group. Based on the NPS, the AUC value was 0.779 for prediction of CKD1–4, 0.684 for prediction of CKD1, and 0.710 for prediction of CKD2. There is still no widely used sensitive instrument for the early identification of CKD. The parameters in the NPS are all commonly and easily measured, suggesting the NPS may have significant value for the early and rapid identification of CKD.

IDO is the rate-limiting enzyme in the kynurenine pathway, a pathway that is upregulated during systemic inflammation. IDO is also considered a critical protein that drives immunotolerance and immunosuppressive responses. A genome-wide association study revealed a potential genetic connection between IDO activity and CKD, and Zhang et al discovered elevated IDO activity in individuals with type 2 diabetic nephropathy.<sup>38,39</sup> Antagonizing IDO was effective in reducing renal fibrosis during CKD, possibly due to the TGF- $\beta$ -mediated tubular epithelial-mesenchymal transition.<sup>40,41</sup> The metabolism of tryptophan by IDO also has a direct or indirect link to atherogenesis, and Walker et al discovered that inhibiting IDO activity could potentially decrease thrombosis in CKD.<sup>42,43</sup> Inhibition of IDO activity could also be helpful for preventing or attenuating ischemia-reperfusion injury.<sup>44</sup> In contrast, Xie et al studied mice with ischemia-reperfusion injury and proposed that IDO increased the proliferation of renal tubular cells, but also limited apoptosis, fibrosis, and secretion of inflammation factors during the self-repair process, an affect achieved through the polarization of macrophages. They also found that dendritic cells that expressed high levels of IDO may alleviate renal injury by decreasing the expression of interleukin-2,6.<sup>45</sup>

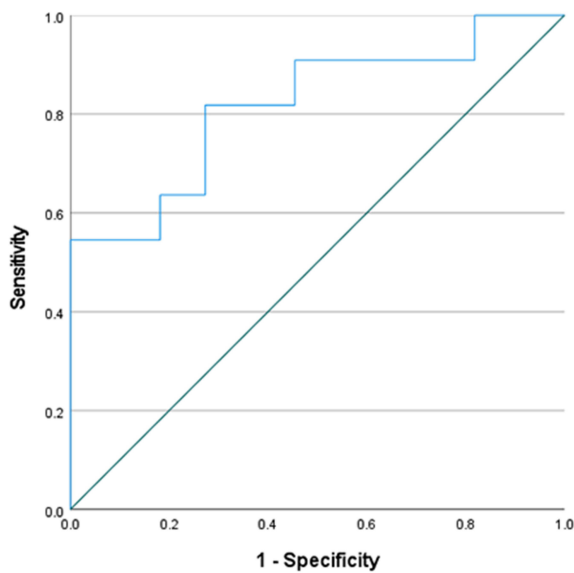
Systemic inflammation and disruption of the immune system have crucial roles in CKD, but no current index has sufficient specificity and sensitivity to evaluate changes in inflammatory status during CKD. Obesity-activated NF- $\kappa$ B is associated with glomerular inflammation and oxidative stress.<sup>46</sup> Hyperglycemia influences the advancement of Diabetic Kidney Disease by elevating interleukin IL-1 $\beta$ , IL-6, and IL-12 levels. Additionally, the abnormal metabolism of glucose and free fatty acids contributes to the progression of Diabetic Kidney Disease by inducing oxidative stress.<sup>47</sup> Endogenous protective factors, such as insulin, VEGF, APC, and GLP-1, could potentially mitigate the negative impacts of hyperglycemia and slow down the advancement of diabetic nephropathy.<sup>48</sup> Therapeutic drugs for diabetic nephropathy, like SGLT2 inhibitors, exhibit nephroprotective effects, while fenelidone demonstrates anti-inflammatory and anti-fibrotic properties that help mitigate the advancement of kidney damage.<sup>49</sup> We found that the NLR and LMR (which



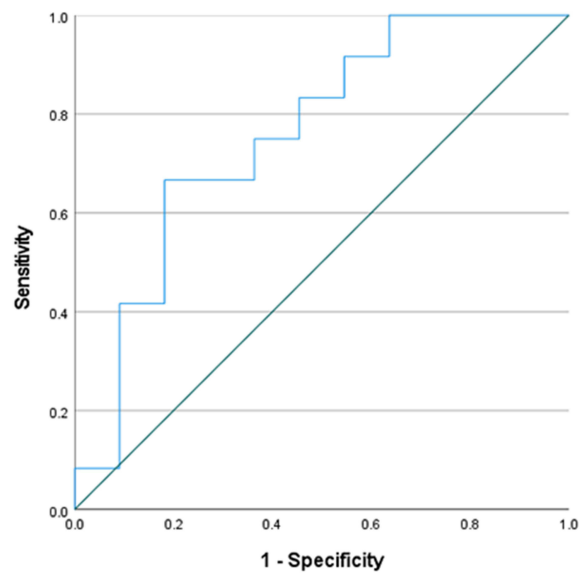
**A**



**B**



**C**



**D**

**Figure 8** Receiver operating characteristic analysis for prediction of Control vs CKD1–4 (A), Control vs CKD1 (B), CKD2 vs CKD3 (C) CKD3 vs CKD4 (D) based on the prediction model.

**Note:** Prediction model:  $CKD = -4.847 + (1.234 \times NPS) + (6.160 \times \text{plasma IDO activity})$ .

**Abbreviation:** CKD, chronic kidney disease.

are part of the NPS) and IDO activity were statistically different between the control group and the CKD1–4 group. Notably, IDO activity had a higher AUC value than urine IDO activity, NLR, and LMR. Most current clinical research on IDO has focused on the role of IDO inhibitors in cancer treatment, and very few studies examined the effect of IDO

inhibitors in CKD. Further laboratory studies and clinical trials that explore the mechanism of IDO in CKD may help to improve the diagnosis and treatment of CKD.

We found that the NPS was significantly different between CKD patients and healthy controls, suggesting that this score may be valuable for prediction of CKD. Furthermore, our results demonstrated significant differences in plasma IDO activity, urine IDO activity, age, urea nitrogen, and uric acid between the healthy controls and CKD1–4 patients. Our logistic regression analysis showed that plasma IDO activity and the NPS were significantly and independently associated with CKD. We therefore used these results to develop a prediction model from these parameters. The OR value of plasma IDO activity was 473.622 in this prediction model, indicating a very strong relationship between plasma IDO activity and CKD. We believe that further investigations of plasma IDO activity and its role in the onset of CKD and the systemic inflammation and altered immune state of these CKD patients has the potential to provide significant benefits for these patients. The prediction model proposed here uses clinical parameters that indicate the inflammatory, immune, and nutritional status of CKD patients. It could therefore be useful for a comprehensive evaluation of the condition of CKD patients, and may also be helpful for the early detection and treatment of CKD.

This study has some limitations that must be addressed. Firstly, it was a single-center study, in that all patients were from the same institution in eastern China. Secondly, the sample size was relatively small. Clearly, studies of larger and more diverse populations are needed for verification of our use of NPS and plasma IDO activity for prediction of CKD sample size for further verification.

Despite these limitations, the CKD prediction model proposed here, which is based on the NPS and plasma IDO activity, has the potential to aid in the early detection, diagnosis, and treatment of CKD.

## Conclusion

A prediction model based on the NPS and IDO provided good to excellent predictions of early-stage CKD.

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## Disclosure

All authors report no conflicts of interest in this work.

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