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Development of a prediction model for in-hospital mortality in immunocompromised chronic kidney diseases patients with severe infection

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Abstract

Background Immunosuppressive agents, although indispensable in the treatment of chronic kidney diseases (CKD), could compromise the patient's immune function. The risk factor for in-hospital mortality in immunocompromised CKD patients with severe infections remain elusive.

Methods We conducted a retrospective analysis of the clinical data of CKD patients who received immunosuppressive agents and presented severe infections. The cohort comprised 272 patients, among whom 73 experienced mortalities during their hospitalization. Logistic regression was employed on the training set to identify key feature variables and construct a predictive model for in-hospital mortality among immunocompromised CKD patients following severe infections. To facilitate clinical application, we constructed a nomogram to visually represent the predictive model.

Results Our findings indicate that ventilator use, vasoactive drug administration, elevated lactate dehydrogenase (LDH), total bilirubin (TBIL) levels, and persistent lymphopenia(PL) are effective predictors of in-hospital mortality in immunocompromised patients with severe infections. These variables were subsequently incorporated to construct a robust prognostic model. Our model demonstrated excellent discriminative ability (AUC = 0.959, 95% CI, 0.924–0.994), significantly outperforming the Sequential Organ Failure Assessment (SOFA) score (AUC = 0.878, 95% CI, 0.825–0.930) and quick Pitt Bacteremia Score (qPBS) (AUC = 0.897, 95% CI, 0.846–0.947). Calibration curve analysis and the Hosmer-Lemeshow (HL) test corroborate the concordance of our model with empirical observations. Furthermore, decision curve analysis (DCA) underscores the superior clinical utility of our predictive model when compared to the SOFA score and qPBS score. Most importantly, our results showed that PL is the most important predictor of in-hospital mortality in immunocompromised patients following severe infection.

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Conclusion Our findings highlight PL as the most significant predictor of in-hospital mortality in immunocompromised CKD patients. A clinical prediction model incorporating PL as a key variable exhibited robust performance in terms of diagnostic accuracy and clinical utility.

Keywords Immunocompromised, Nomogram, SOFA score, Persistent Lymphopenia

Introduction

Immunosuppressive drugs are currently the most commonly used in the treatment of chronic kidney disease (CKD). However, both long-term use of immunosuppressive drugs and the primary disease can lead to immune system dysfunction. Previous studies show that infection is a major risk factor for death in immunocompromised individuals, possibly due to their altered immune responses to pathogens compared to those with normal immune function [1, 2]. Currently, the Sequential Organ Failure Assessment score (SOFA) is used to assess the severity of sepsis, and the quick Pitt Bacteremia score (qPBS) score for bloodstream infection severity [3, 4]. These tools are designed for individuals with normal immune function. Therefore, there is an ongoing demand for a simple and effective model to assess the severity of the condition in immunocompromised CKD patients following severe infection.

In this study, we retrospectively analyzed the clinical characteristics and laboratory results of immunocompromised CKD patients who were hospitalized due to severe infections. We initially screened significant predictors of in-hospital mortality using logistic regression and constructed a clinical prediction model. A nomogram was used to visualize the model. The performance of the model was evaluated using receiver operating characteristic (ROC) curves, decision curve analysis (DCA), and calibration curves. The results showed that our model outperformed the SOFA score and qPBS score in predicting mortality among immunosuppressed CKD patients with severe infections. Furthermore, we found that PL was the most important predictor of mortality, with patients experiencing PL having a significantly higher mortality rate than those who did not, thus clarifying the clinical significance of this indicator.

To the best of our knowledge, this will be the first nomogram to assess the severity of the disease in immunocompromised CKD individuals after severe infection. We aim to provide evidence-based support for clinical decision-making in these patients through our model.

Methods

Study design and participants

Inclusion criteria

Our study incorporated CKD patients who were treated for severe infections at the National Clinical Research Center of Kidney Diseases at the Jinling Hospital due to severe infections while receiving immunosuppressive therapy from January 2012 to January 2024. The criteria for immunocompromised included patients with primary chronic kidney diseases necessitating long-term use of immunosuppressants, such as IgA nephropathy, membranous nephropathy and minimal change disease, et cetera; individuals with autoimmune diseases requiring long-term immunosuppression, including lupus nephritis (LN), ANCA-associated vasculitis, and anti-glomerular basement membrane disease (anti-GBM disease); kidney transplant recipients. Long-term use of immunosuppressants was defined as use for more than three months, and included drugs such as corticosteroids, tacrolimus, cyclosporine, and mycophenolate mofetil, et cetera. The diagnosis of severe infection was defined as requiring hospital admission for intravenous antibiotic treatment [5–7]. The pathogens were identified through cultures of bodily fluids such as blood, bronchoalveolar lavage fluid, cerebrospinal fluid, or through metagenomic next-generation sequencing (mNGS).

Exclusion criteria

Immunocompetent patients. Clinical data is largely missing.

Diagnostic and scoring criteria

Persistent lymphopenia (PL) is diagnosed based on established studies, with a persistent lymphocyte count below 400/μl for a minimum of four days. SOFA score according to the SOFA scoring criteria proposed in the sepsis 3.0 definition [3]. The qPBS score criteria refer to previous studies [4].

Data analysis

All statistical analyses in our study were performed using SPSS 26 (IBM Corporation) and R software (version 4.0.3; http://www.r-project.org). General data with excessive missing values were excluded (proportion exceeds 10%), while partially missing important data (proportion less than 5%) were imputed using multiple imputation methods. The significance level for all reported statistics was set at $p < 0.05$ for two-tailed tests. Statistical analysis of demographic characteristics, underlying diseases, clinical manifestations, and laboratory parameters was conducted using SPSS. Normally distributed continuous variables were presented as mean ± SD, non-normally distributed as median (interquartile range), and categorical variables as percentages. Continuous variables following normal distribution were analyzed using independent

sample student's t-tests, non-normally distributed variables were assessed with non-parametric rank sum tests, and categorical variables were evaluated using chi-square tests.

We randomly divided the included patients into a training set and a validation set at a ratio of 3:1 using R software (the *car* package and the *survival* package), ensuring that there were no statistically significant differences in clinical characteristics between the two sets. In the training cohort, the potential prognostic variables of $p < 0.05$ in univariate logistic analysis were included in the multivariable analysis. Then, multivariable logistic regression analysis was used to identify the independent risk factors for the in-hospital mortality rate. All the predictors were employed to develop a nomogram predictive model.

To evaluate our predictive model, we constructed Receiver Operating Characteristic (ROC) curves for both training and validation sets, using Area Under the Curve (AUC) as the primary metric for assessing discriminative ability. The model's calibration was appraised through the Hosmer-Lemeshow (HL) test, and we plotted calibration curves to demonstrate the agreement between predicted outcomes and actual observations. Lastly, Decision Curve Analysis (DCA) was performed to assess the clinical utility of the model, quantifying the net benefit across various risk thresholds.

We used the mice package in R for multiple imputations. For data visualization, the *rms* package in R was used for nomogram and calibration plots, the *pROC* package for ROC curves and AUC calculation, and the *rmda* and *ggDCA* packages for plotting decision curves. This comprehensive suite of tools facilitated a robust and detailed evaluation of the predictive model's performance.

Results

Clinical characteristics among immunocompromised CKD patients after severe infection

A total of 302 patients were initially included, with exclusions made for those not immunocompromised, those with incomplete data, or absence of pathogen information. Ultimately, 272 patients were included (Fig. 1).

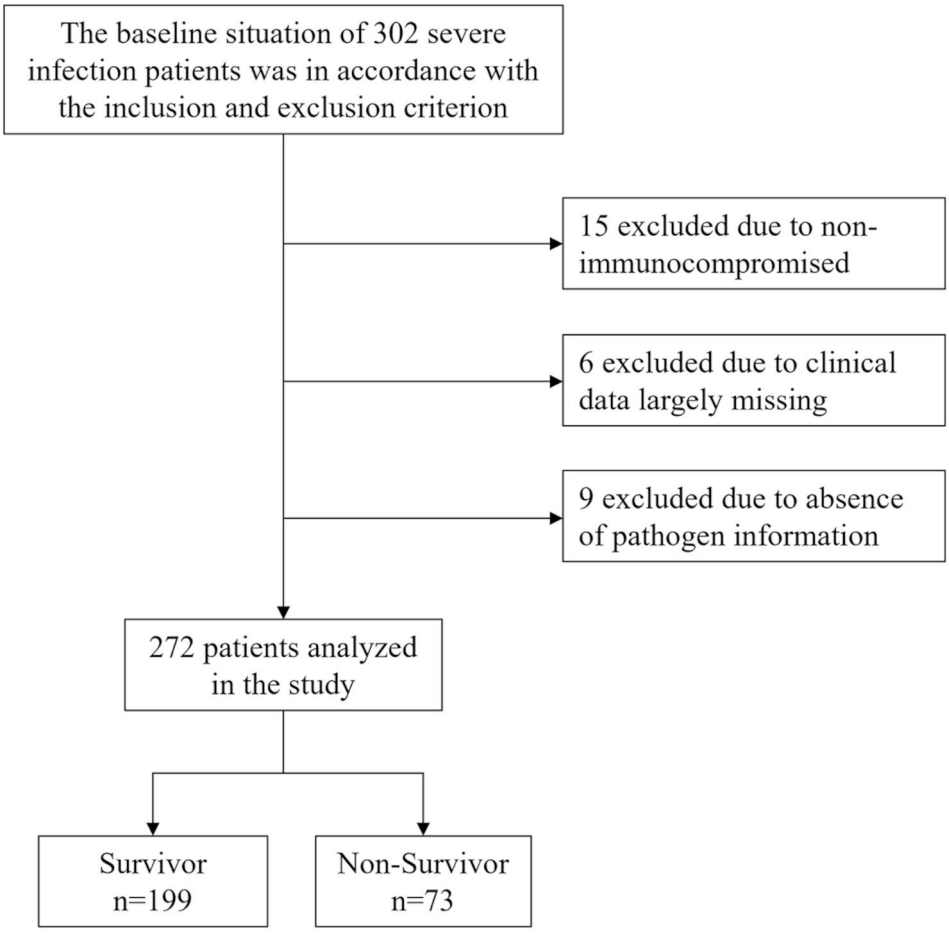

Fig. 1 Flowchart of patient selection. From 302 immunocompromised patients following severe infection was in accordance with the inclusion and exclusion criterion, 272 were eligible for inclusion. Patients were excluded due to non-immunocompromised ($n = 15$), clinical data largely missing ($n = 6$), absence of pathogen information ($n = 9$)

Among the 272 patients, there were 125 cases of primary chronic kidney diseases, 66 cases of autoimmune diseases, including 55 cases of LN, 10 cases of ANCA-associated vasculitis, and 1 case of Sjögren's syndrome. There were also 81 cases of Kidney transplant recipient (Supplement Table 1).

There were 73 non-survivors and 199 survivors during hospitalization. In terms of vital signs, compared to the survivor group, the non-survivor group was older, and had lower Glasgow Coma Scale (GCS) scores. Laboratory tests showed significantly higher levels of C-Reactive Protein (CRP), interleukin-6 (IL-6), alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin (TBIL), LDH and N-terminal pro b-type natriuretic peptide (proBNP) in the non-survivor group, while fibrinogen (FIB) levels were lower. Additionally, non-survivor group had lower absolute lymphocyte count (ALC), CD4 + and CD8 + T lymphocytes count and a higher incidence of PL. In terms of infection types, patients with pulmonary infections had a higher mortality rate, while those with fungal or viral infections also had elevated mortality rates. The usage of organ support therapy such as mechanical ventilation, vasoactive drugs, and renal replacement therapy was more frequent in the non-survivor group (Table 1).

Development of a prediction model in immunocompromised CKD patients after severe infection

Next, patients were randomly divided into a training set ($n = 204$) and a validation set ($n = 68$) at a 3:1 ratio. Statistical analysis revealed no significant differences in various indicators between the two groups (Supplement Table 2). Then, univariate logistic regression was initially performed to identify clinically significant variables among 23 potential predictors. Variables with a p-value less than 0.05 were included in a multivariate logistic regression model. Based on the odds ratios (OR) and p-values ($p < 0.05$), variables "TBIL", "LDH", "PL", "Use of Ventilation" and "Use of vasoactive drugs" were ultimately identified as independent predictors of all caused in hospital mortality (Table 2). Finally, we used a nomogram to illustrate the regression model based on the above independent variables (Fig. 2a). According to the nomogram, we can obtain the scores corresponding to each predictive variable and record the sum of these scores to provide an accurate prediction of in hospital mortality risk in immunocompromised patients after severe infection. For instance, a patient who experienced PL would score 40 points for this variable (top points segment). If this patient also received ventilation and vasoactive drugs, they would score 20 and 19 points, respectively, resulting in a total score of 79 (bottom total points segment). The corresponding mortality rate at 79 points on the total points segment is 70%, indicating a high risk of death for this patient.

Evaluation and validation of prediction model in immunocompromised CKD patients after severe infection

We evaluated the predictive efficiency of this model using ROC curves, as shown in Fig. 2b and d. The AUC of the training group was 0.959 (95% CI: 0.924 ~ 0.994), and the AUC of the validation set was 0.956 (95% CI: 0.882 ~ 1.000), indicating that the model has strong predictive capability. Next, we employed calibration curves to evaluate the agreement between predictions and observations of our model, as shown in Fig. 2c and e, our model showed good calibration. Finally, the Hosmer-Lemeshow goodness-of-fit test indicated P-values greater than 0.999, reflecting a high degree of alignment between the model's predicted probabilities and the observed outcomes.

To further evaluate the diagnostic efficiency of this model, we conducted a comparison with the SOFA score and the qPBS score. In the training set, when using the SOFA score to predict patient outcomes, the AUC was 0.878 (95% CI, 0.825 ~ 0.930), while using the qPBS score, the AUC was 0.897 (95% CI, 0.846 ~ 0.947). We employed the DeLong test to assess the SOFA score, qPBS score, and our model separately. The results indicated that our model significantly outperformed both the SOFA score (AUC_{Model} vs. AUC_{SOFA}=0.959 vs. 0.878, $p < 0.001$) and the qPBS score (AUC_{Model} vs. AUC_{qPBS}=0.959 vs. 0.897, $p = 0.003$) in terms of prognostic prediction efficiency. Next, we employed DCA to access the net benefit of our model. The result showed that our model demonstrated a consistently higher DCA curve across all threshold values compared to the SOFA and qPBS scores. This indicates that, relative to SOFA and qPBS, our model can identify a larger proportion of high-risk patients, thereby enabling more aggressive treatment strategies (at lower threshold values). Moreover, when high-risk patients are identified and managed based on our model, it leads to better outcomes while effectively avoiding false positives and unnecessary treatments (at higher threshold values). (Fig. 2f and g)

The impact of persistent lymphopenia on in-hospital mortality in immunocompromised CKD patients following severe infections

We found that, in our constructed model, most indicators except for the PL were included in the SOFA score. Therefore, we combined the PL with the SOFA score to construct a new model and compared it with the SOFA score alone. The results indicated that the model combining PL and SOFA scores exhibited a higher diagnostic efficiency compared to the SOFA score alone

Table 1 The demographics and clinical characteristics of immunocompromised CKD patients after severe infection

Variables	Total(*n* = 272)	Survivor(*n* = 199)	Death(*n* = 73)	p_value
Basic Information				
Age(years)	46.36 ± 17.10	44.66 ± 16.47	51.01 ± 18.02	0.006
Gender(Male, *n*, %)	161(59.2%)	120(60.3%)	41(56.2%)	0.538
Diabetes(*n*, %)	57(21.0%)	44(22.1%)	13(17.8%)	0.440
Hypertension(*n*, %)	75(27.6%)	52(26.1%)	23(31.5%)	0.379
CKD1(*n*, %)	91(33.5%)	66(33.2%)	25(34.2%)	0.867
CKD2(*n*, %)	44(16.2%)	35(17.6%)	9(12.3%)	0.297
CKD3(*n*, %)	92(33.8%)	65(32.7%)	27(37.0%)	0.504
CKD4(*n*, %)	29(10.7%)	21(10.6%)	8(11.0%)	0.923
CKD5(*n*, %)	16(5.9%)	12(6.0%)	4(5.5%)	0.864
Laboratory Parameters				
WBC (*10^9)	9.1(5.57–13.44)	9.3(5.47–13.94)	8.7(5.83–12.79)	0.483
NEUT (%)	88.0(80.60-92.85)	87.2(80.5–91.9)	89.4(80.45–93.60)	0.262
Lym (*10^9)	0.54(0.25-1.00)	0.59(0.318–1.11)	0.4(0.18–0.90)	0.012
HGB (g/L)	101 ± 26	101 ± 25	101 ± 29	0.928
PLT (*10^9)	152(88–219)	154(91–223)	139(66–201)	0.201
CRP (mg/L)	158.3 ± 87.9	150.1 ± 87.1	180.7 ± 86.7	0.011
Alb(g/L)	24.6 ± 6.8	24.7 ± 7.0	24.4 ± 6.3	0.748
Glb(g/L)	24.0 ± 7.8	24.5 ± 7.6	22.5 ± 8.1	0.062
PCT(μg/L)	6.05(0.97–37.72)	5.34(0.82–39.27)	7.01(1.53–34.26)	0.227
IL6(ng/L)	137.60(43.52–445.30)	123.40(41.03–352.70)	243.5(63.51–854.10)	0.005
FIB (g/L)	4.71(3.58–5.88)	4.83(3.80–6.12)	4.54(3.04–5.20)	0.008
ALT(U/L)	36(24–67)	33(23–57)	45(24–85)	0.004
AST(U/L)	37(25–65)	34(22–52)	57(35–89)	0.000
TBIL(μmol/L)	7.2(3.4–12.9)	6.6(3.3–11.1)	9.6(3.6–41.9)	0.001
LDH (U/L)	763(449–1270)	717(432–1033)	1112(622–2036)	0.000
proBNP(pmol/L)	784(159–2733)	749(100–2174)	1901(421–3970)	0.003
CD4 (cells/μl)	139(70–313)	160(93–351)	76(28–213)	0.000
CD8 (cells/μl)	140(62–262)	157(80–310)	80(35–179)	0.000
PL(*n*, %)	76(27.9%)	19(9.5%)	57(78.1%)	0.000
Organ Support				
CRRT(*n*, %)	150(55.1%)	86(43.2%)	64(87.7%)	0.000
Vasoactive Drugs (*n*, %)	93(34.2%)	32(16.1%)	61(83.6%)	0.000
Ventilation(*n*, %)	108(39.7%)	45(22.6%)	63(86.3%)	0.000
Infection Status				
BloodInfect(*n*, %)	172(63.2%)	132(66.3%)	40(54.8%)	0.080
LungInfect(*n*, %)	145(53.3%)	89(44.7%)	56(76.7%)	0.000
OtherInfect(*n*, %)	39(14.3%)	33(16.6%)	6(8.2%)	0.081
G^+ (*n*, %)	50(18.4%)	39(19.6%)	11(15.1%)	0.393
G^- (*n*, %)	150(55.1%)	106(53.3%)	44(60.3%)	0.303
Fungal (*n*, %)	110(40.4%)	69(34.7%)	41(56.2%)	0.001
Virus(*n*, %)	63(23.2%)	37(18.6%)	26(35.6%)	0.003
Disease severity score				
GCS	14(8–15)	14(14–15)	6(6–10)	0.000
SOFA	8 ± 5	6 ± 4	13 ± 4	0.000
qPBS	3 ± 3	2 ± 2	6 ± 3	0.000

CKD: Chronic Kidney Diseases; GCS: Glasgow Coma Scale; PL: Persistent Lymphopenia; CD4: Absolute CD4 + Lymphocyte Count; CD8: Absolute CD8 + Lymphocyte Count; BloodInfect: Blood Infection; LungInfect: Lung Infection; OtherInfect: Other Infection; G^+: Gram-positive bacteria; G^-: Gram-negative bacteria; SOFA: Sequential Organ Failure Assessment Score; qPBS: quick Pitt Bacteremia Score

($AUC_{PL+SOFA}$ vs. AUC_{SOFA} = 0.942 vs. 0.878, $p = 0.003$). (Fig. 3a and b)

Our model revealed that PL was the most strongly associated with in-hospital mortality in immunocompromised CKD patients with severe infections, as evidenced by its highest odds ratio (OR). Then, we employed Kaplan-Meier survival analysis to investigate the impact of PL on survival outcomes (Fig. 3c). The

Table 2 Identification of risk factors for in-hospital mortality in immunosuppressed CKD patients after severe infections

Variable	Univariable OR (95% CI)	*p*_value	Multivariable OR (95% CI)	*p*_value
Age(years)	1.024(1.005–1.044)	0.013		
GCS	0.682(0.616–0.755)	0.000		
CRP(mg/L)	1.003(1.000-1.007)	0.079		
IL6(ng/L)	1.000(1.000–1.000)	0.706		
FIB (g/L)	1.026(0.949–1.11)	0.521		
ALT(U/L)	1.003(1.000-1.007)	0.088		
AST(U/L)	1.004(1.001–1.007)	0.018		
TBIL(μmol/L)	1.039(1.017–1.062)	0.000	1.037(1.005–1.069)	0.022
LDH (U/L)	1.001(1.000-1.001)	0.001	1.001(1.000-1.001)	0.014
proBNP(pmol/L)	1.000(1.000–1.000)	0.037		
CD4(cells/μl)	0.997(0.995–0.999)	0.004		
CD8(cells/μl)	0.996(0.994–0.999)	0.004		
PL(n,%)	42.079(17.438-101.534)	0.000	30.61(106.502–8.798)	0.000
CRRT(n,%)	7.646(3.373–17.333)	0.000		
Vasoactive Drugs (n,%)	3.657(1.811–7.385)	0.000	6.224(21.723–1.783)	0.004
Ventilation(n,%)	26.956(10.619–68.426)	0.000	7.236(25.220–2.076)	0.002
LungInfect(n,%)	3.657(1.811–7.385)	0.000		
Fungal(n,%)	2.277(1.205–4.302)	0.011		
Virus(n,%)	3.412(1.710–6.807)	0.000		

GCS: Glasgow Coma Scale; PL: Persistent Lymphopenia; CD4: Absolute CD4 + Lymphocyte Count; CD8: Absolute CD8 + Lymphocyte Count; LungInfect: Lung Infection

results showed a significantly higher in-hospital mortality rate among patients in the PL group compared to those in the non-PL group ($p < 0.001$).

Discussion

The proportion of immunocompromised CKD population among critical care patients is continuously increasing. Typical immunocompromised states include patients requiring oral immunosuppressive therapy for more than 3 months for primary disease, autoimmune diseases, and solid organ transplant recipients [2]. Both the primary diseases and the pharmacological interventions significantly affect patients' innate and adaptive immune function. It is widely recognized that the immune response to pathogens, rather than the pathogens themselves, is the main driving factor for the development of life-threatening organ dysfunction after infection [8]. Immunocompromised patients, due to their altered pathogen-immune system interactions, often present different clinical manifestations compared to immunocompetent individuals. In previous clinical research on sepsis, populations with immunosuppression were often excluded from the study cohort, but our research focuses specifically on this group of patients. We collected clinical and laboratory data of immunocompromised CKD patients treated for severe infections at the National Clinical Research Center of Kidney Diseases at the Jinling Hospital from January 2012 to January 2024. By using logistic regression, we identified relevant indicators and constructed a nomogram to establish a novel predictive model for the prognosis of severe infections in immunocompromised patients, demonstrating superior performance over the SOFA score and qPBS score. This is the first nomogram on the prognosis of severe infection in immunocompromised patients.

Previous studies have explored bloodstream infections in immunocompromised patients, revealing that age over 60 years and increased procalcitonin levels are independent predictors of mortality within 60 days post-infection [8]. However, these studies encompassed a diverse range of immunocompromised conditions including solid tumors, hematological disorders, transplants, autoimmune diseases, diabetes, cirrhosis, post-surgical critical illnesses, and burns, thereby leading significant heterogeneity. Florence et al. reported on ICU-acquired infections in 98 patients with systemic rheumatic diseases receiving immunosuppressive therapy, with a hospital mortality rate of 17.3%. Renal replacement therapy and mechanical ventilation were independent predictors of mortality [9]. Andry et al. conducted a retrospective study on patients with impaired immune function and concomitant acute respiratory failure, and the results suggested that the population with bacteremia had a higher proportion of hematological malignancies and higher SOFA scores, as well as a greater need for organ support. Bacteremia was associated with higher ICU crude mortality rate, but not with in-hospital mortality rate or 90-day mortality rate [10]. Previous studies have already demonstrated that the use of mechanical ventilation, vasoactive drugs, and TBIL are independent risk factors for in-hospital mortality in critical care patients, and these factors are incorporated into the SOFA score [11, 12]. Our study also included

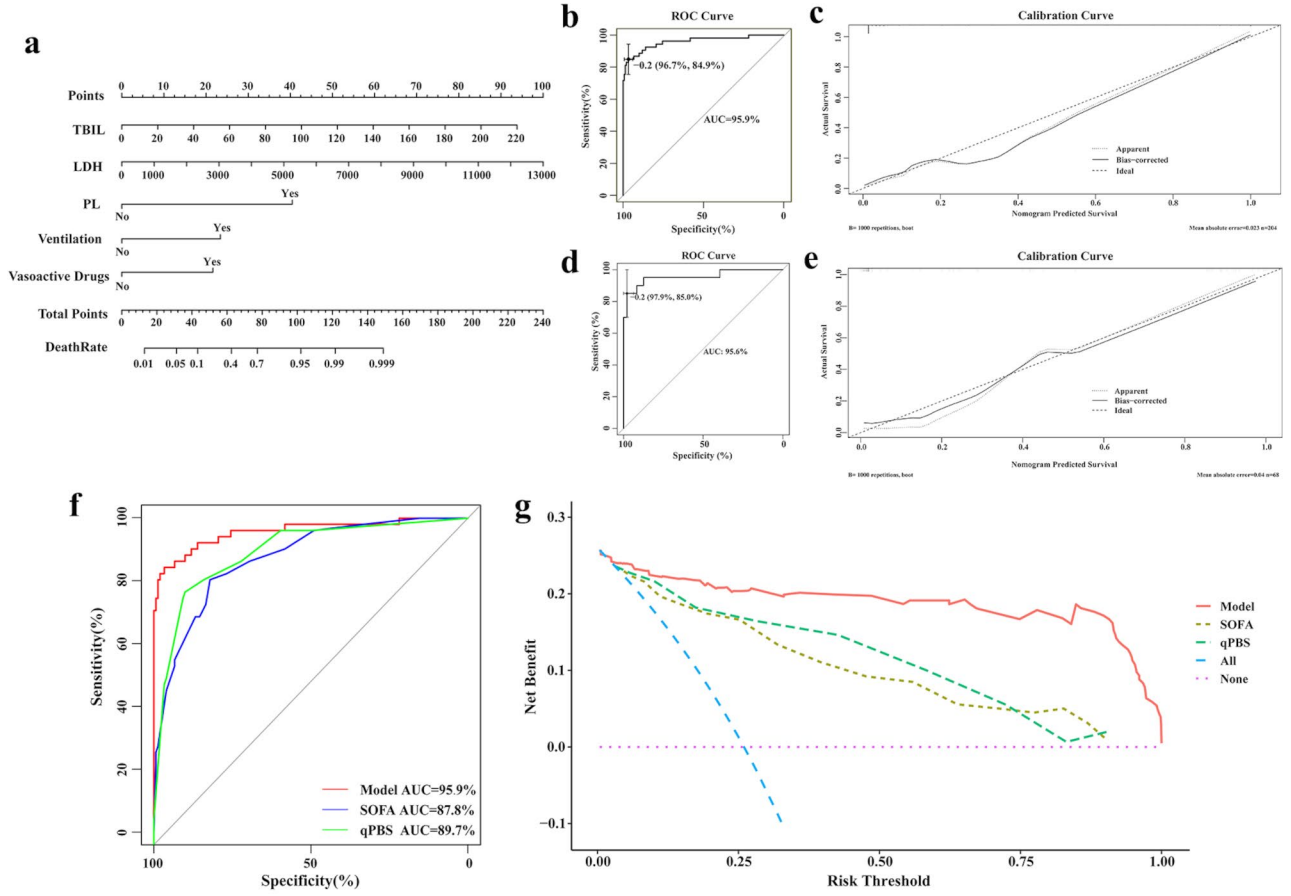

Fig. 2 Construction and evaluation of a clinical model for predicting in-hospital mortality in immunocompromised CKD patients following severe infections. (**a**) The nomogram was constructed to illustrate the regression model based on the above independent variables identified by univariate and multivariate analysis. (**b & d**) The model's predictive efficiency is evaluated using ROC curves in the training set (**b**) and validation set (**d**), with an AUC of 0.959 (95% CI: 0. 0.924 ~ 0.994) in the training set, and an AUC of 0.956 (95% CI: 0.882 ~ 1.000) in the validation set. (**c & e**) The calibration curves for both the training (**c**) and validation (**e**) sets demonstrate that the model exhibits good calibration, with a closer fit to the diagonal dashed line representing an ideal evaluation by a perfect model. (**f**) ROC curve to compare the discriminative performance of our model (Model) with SOFA score and qPBS score (AUC_{Model} vs. AUC_{SOFA} = 0.959 vs. 0.878, $p < 0.001$; AUC_{Model} vs. AUC_{qPBS} = 0.959 vs. 0.897, $p = 0.003$). (**g**) DCA curves to compare the clinical net benefits of our model with the SOFA score and qPBS score. PL: Persistent lymphopenia; LDH: Lactate Dehydrogenase; TBIL: total bilirubin

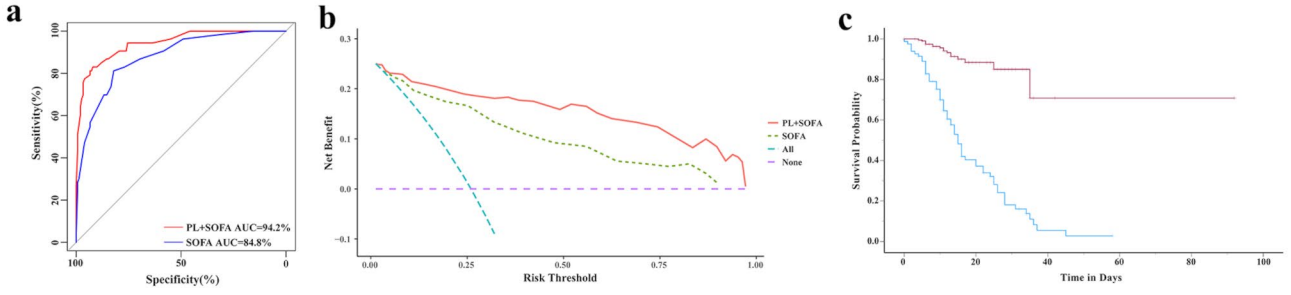

Fig. 3 Persistent lymphopenia is the most significant risk factor for predicting in-hospital mortality in immunocompromised CKD patients following severe infections. (**a**) ROC curves to compare the discriminative performance and clinical net benefits of SOFA score and SOFA plus PL model ($AUC_{PL+SOFA}$ vs. AUC_{SOFA} = 0.942 vs. 0.878, $p = 0.003$). (**b**) DCA curve showed that the SOFA plus PL model had a higher net benefit than the SOFA score in predicting the in-hospital mortality. (**c**) Survival analysis results for patients in the PL group and non-PL group. Kaplan-Meier survival analysis showed a significantly higher in-hospital mortality rate among patients in the PL group compared to those in the non-PL group ($p < 0.05$). PL: Persistent lymphopenia

the TBIL level, the application of vasoactive drugs, and mechanical ventilation. This conclusion indicates that severe respiratory and circulatory also represent significant risk for mortality following severe infections in immunocompromised CKD patients.

In our study, we incorporated PL as one of the significant indicators for predicting our patient prognosis. However, the definition of PL remains non-standardized. Drewry et al. investigated PL in patients with normal immune function who developed sepsis. They defined severe lymphocytopenia as an absolute lymphocyte count (ALC) below 600 cells/μl and proposed a duration of four days to classify it as persistent, based on evidence suggesting a significantly reduced mortality risk when ALC returns to normal within four days [13]. Similarly, another study investigating the outcomes of critical care patients following emergent surgery identified a correlation between increased survival rates and the normalization of ALC by the fifth day [14]. In the context of immunocompromised individuals, severe lymphocytopenia has been characterized as an ALC ranging between 300 and 500 cells/μl [6, 15]. For the purposes of our study, we have defined PL as an ALC of less than 400 cells/μl persisting for a duration of four days.

Lymphocytes, including T cells, B cells, and natural killer cells, are essential components of the human immune system. These cells are responsible for antibody production, direct cell-mediated killing of virus-infected and tumor cells, and regulation of the immune response. Previous studies have consistently demonstrated that lymphopenia reflects an impairment of the adaptive immune system and is associated with an increased risk of infection and higher in-hospital mortality rates following severe infections. Adrie et al. showed that PL predicted increased 28-day mortality in ICU patients [16]. Jing et al. concluded in a retrospective cohort study that septic patients with PL have higher mortality, worse conditions, increased risk of secondary infection, and poor prognosis regardless of shock [17]. Adigbli et al. extracted conclusions from two ICU patients' databases that PL is common in critically ill patients and associated with increased risk of death [18]. Furthermore, Research has indicated that reversing lymphopenia can improve patient outcomes. Intravenous administration of CYT107(a glycosylated recombinant human IL-7) resulted in a two-threefold increase in absolute lymphocyte counts, and was associated with increase in organ support free days [19].

Numerous studies have explored the causes of PL. In our patient cohort, the occurrence of PL could be attributed to several factors: (1) Primary disease induced PL: For instance, Patients with SLE often exhibit T cell dysfunction, particularly an increased proportion of exhausted T cells [20], decreased IL-2 secretion [21], and a breakdown of B cell tolerance mechanisms leading to polyclonal activation and production of numerous autoantibodies [22]. Research indicates that in SLE patients, the RNA-binding protein serine/arginine-rich splicing factor 1 (SRSF1) is associated with lymphocyte reduction. Overexpression of SRSF1 can rescue the survival of T cells in SLE patients [23]. (2) Medication-induced PL: Previous studies have demonstrated that the use of various immunosuppressants, especially glucocorticoids, is the most significant risk factor affecting patients' innate and adaptive immunity. Chen et al. explored the impact of glucocorticoids on lymphocytes in the nephrotic syndrome population. They found that glucocorticoids inhibit the mTORC1 pathway through DNA methylation, FOXP3 upregulation, and ultimately exert a long-term suppressive effect on lymphocytes by regulating T cells [24]. (3) Severe Infections: The inability to eradicate persistent pathogens may result in the prolonged suppression of immune function. Studies have shown that persistent viral infections can induce T cell exhaustion, characterized by high expression of immunological checkpoint inhibitors such as PD1 and Tim3, thereby producing a suppressive effect [25, 26]. Huang et al. showed that in sepsis patients, Tim3 expression is increased on $CD4^+$ T lymphocytes. This increase could inhibit the NFκB pathway through binding with the ligand HMGB1, and lead to reduced proliferative capacity and increased expression of inhibitory markers in T cells [27]. Damien et al. explored the expression of exhaustion-related markers on $CD8^+$ T lymphocytes in sepsis patients. They found that $CD8^+$ T lymphocytes with immunological characteristics of $2B4^{hi}PD\text{-}1^{hi}CD\text{-}160^{low}$ and $2B4^{hi}PD\text{-}1^{low}CD160^{hi}$ showed abnormal cytokine production and were associated with an increased risk of death [28]. In our patient cohort, the incidence of viral and fungal infections was higher in the death group, raising the question of whether this led to T lymphocyte exhaustion and subsequent persistent lymphocyte reduction, a topic warranting further exploration.

Our predictive model also incorporated LDH as a significant indicator. Under hypoxic conditions, cells generate energy through anaerobic metabolism, where LDH catalyzes the conversion of lactate to pyruvate, providing energy via lactate fermentation. Previous research has explored the relationship between LDH and mortality in patients with sepsis. A study by Liang et al. indicated that the serum LDH to albumin ratio (LAR) is significantly associated with both in-hospital and long-term adverse outcomes in patients with sepsis-related acute kidney injury [29]. Research conducted by Tang et al. demonstrates that within immunocompromised patients, elevated levels of LDH serve as a crucial indicator for prognostic assessment of pneumocystis jirovecii pneumonia [30]. In our study population, we observed a

higher breath rate among patients in the mortality group. We hypothesize that such patients are more prone to hypoxia, and consequently, elevated levels of LDH are a significant factor in predicting mortality. However, further validation with a larger sample size is required.

The accessibility of inclusion indicators is also a key standard for evaluating the clinical utility of a model. The included indicators such as TBIL and LDH can be obtained from routine clinical biochemical tests and are part of the routine admission examinations, which are convenient for clinical application. PL requires dynamic monitoring of the patient's complete blood count after admission, which is also a routine examination for critically ill patients after admission. Although this requires multiple monitoring within the first week of admission and may increase the medical burden, we believe it is worthwhile for critically ill patients with severe infections. We have included the use of mechanical ventilation and vasoactive drugs, which only require accurate clinical recording and are also easily obtained data.

However, this study has some potential limitations. As a retrospective study, selection bias and the exclusion of patients with missing data may have influenced our results. Although we compared the included data with the excluded patients' data and found no statistically significant differences, analysis of larger-scale clinical data is still necessary, which is ongoing in our current work. Additionally, the data included in this study were from a single center and were not externally validated with data from other centers, which may also affect the applicability of our model to a broader population, although we have validated the reliability of the model in a validation set. In the future, we will validate the model based on publicly available databases and conduct prospective multicenter studies to further verify its reliability. Third, although the patients included in this study were based on the current mainstream definition of immunosuppressed status, it is undeniable that there is heterogeneity among the population we included, such as the impact of primary diseases and previous treatments on patient status. Although our sample size is relatively large, which may mitigate the impact of this heterogeneity on the results to some extent, and our results suggest that PL appears to have a significant impact on the prognosis of patients with severe infections regardless of their immunosuppressive status, in-depth exploration of single diseases is still necessary in the future, which we are currently undertaking. Fourth, our study lacks long-term follow-up data. Since the main focus of this study is to explore the in-hospital status of patients, severe infections may have an impact on the long-term prognosis and quality of life of immunosuppressed kidney disease patients, which is also a topic worthy of attention. We will further explore this issue in future studies.

In conclusion, we identified risk factors for in-hospital mortality following severe infection in immunocompromised CKD patients and visualized these through a Nomogram. This model demonstrates superior predictive efficiency compared to both the SOFA score and the qPBS score. To our knowledge, this is the first prognostic prediction model specifically designed for severe infections in immunocompromised CKD patients.

Supplementary Information

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Supplementary Material 1

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None.

Author contributions
Shijun Li contributed to the conception of the study; Yang Wang and Yuchao Zhou prepared the figures and wrote the manuscript; Liang Zhao and Chunni Huang performed the data analyses; Lixuan Lou contributed to the follow-up work; Mingzhu Zheng helped perform the analysis with constructive discussions.

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Data availability
The data supporting the findings of this study are not publicly available, as they contain information that could compromise the privacy of research participants. They are available from the corresponding author, Shijun Li, upon reasonable request.

Declarations

Statement of Ethics
The experimental protocol was established, according to the ethical guidelines of the Helsinki Declaration and ethics approval was obtained from the Jinling Hospital, Nanjing University School of Medicine (2021NZKY-032-01). Written informed consent was waived due to the retrospective noninterventional design.

Clinical trial number
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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