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Association Between Red Blood Cell Distribution Width and Prognosis of Renal Transplant Recipients with Early-Onset Pneumonia

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Background: Following renal transplantation, early-onset pneumonia is a frequent and severe infection-related complication. Red blood cell distribution width (RDW) has been reported as a predictive marker among patients with infectious diseases. Therefore, the aim of this study was to explore the significance of RDW in predicting prognosis, including 60-day mortality, in renal transplant recipients with early-onset pneumonia.


Material/Methods: Clinical data from patients who developed early-onset pneumonia after renal transplantation were retrospectively reviewed. Patients were divided into 2 groups: those with an RDW $\leq 15.0\%$ and those with an RDW $> 15.0\%$. The 60-day mortality, bacteremia, need for mechanical ventilation, renal transplant rejection rate, and number of admissions to the intensive care unit (ICU) were estimated by Kaplan-Meier methods. Univariate and multivariate Cox regression analyses were performed to determine the risk factors for 60-day mortality.

Results: Among the 118 patients participating in the study, 18 (15.2%) died during the 60-day follow-up. Kaplan-Meier analysis showed a death rate of 9.38% in the group with an RDW $\leq 15.0\%$, and a death rate of 40.9% in the group with an RDW $> 15.0\%$ ($P < 0.001$). Patient prognosis, including episodes of mechanical ventilation, graft rejection, and ICU admissions were significantly different between groups ($P < 0.01$). RDW was an independent factor related to higher 60-day mortality (HR, 1.672; 95% CI, 1.111–2.516).

Conclusions: Among patients with early-onset pneumonia following renal transplantation, increased RDW $> 15.0\%$ was significantly associated with prognosis and 60-day mortality.

MeSH Keywords: **Erythrocyte Indices • Kidney Transplantation • Pneumonia**

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Background

Renal transplant recipients are routinely treated with immunosuppressive therapy, which makes them susceptible to infection. Postoperative infection is the second leading cause of death following renal transplant in the USA [1]. Pneumonia is a frequent cause of death among kidney transplant recipients, usually requiring intensive care and incurring high medical costs. Recovery of immune status is commonly delayed until 6 months post-transplantation, and the morbidity and mortality from early-onset pneumonia within this 6-month period are greater than in late-onset pneumonia [2]. The incidence of pneumonia in renal transplant recipients ranges from 8.8% to 20.0% [3], and the mortality rate in this group ranges from 10% to 30% [4]. Despite the poor prognosis of early-onset pneumonia in renal transplant recipients, there is no single predictive or prognostic biological marker for pneumonia.

Red blood cell distribution width (RDW) is the range of variation in sizes or shapes of red blood cells (RBC), reported in routine blood tests. RDW is an indicator reflecting the heterogeneity of red blood cell volume, which is expressed as the ratio of the mean corpuscular volume (MCV) to standard deviation (SD) of erythrocyte volume [5]. The RDW was initially shown to be an important laboratory index in the diagnosis of iron-deficiency anemia [6]. Increased RDW was recently documented to be closely linked to poor prognosis in several cardiovascular diseases, including acute coronary syndrome [7], heart failure [8,9], atrial fibrillation [10], myocardial infarction (MI) [11], ischemic cerebrovascular disease [12], pulmonary hypertension [13], peripheral artery disease (PAD) [14], and acute stroke [15]. A high RDW has also been linked to elevated mortality of cancer patients [16]. Recently, increased RDW was shown to be a strong independent predictor of incremental mortality rate among patients with infectious or inflammatory diseases, including community-acquired pneumonia [17], gram-negative bacteremia [18], severe sepsis [19], and acute respiratory distress syndrome (ARDS) [20]. The fundamental mechanisms of the correlation between the RDW and prognosis among patients with pneumonia remain unclear, and the role of the RDW as a marker of patient outcome following renal transplantation, including mortality, is also unknown. Therefore, the present study explored the significance of RDW in predicting prognosis, including 60-day mortality, in renal transplant recipients with early-onset pneumonia.

Material and Methods

Patients

We retrospectively analyzed 118 patients enrolled over 18 years old who developed early-onset pneumonia within 6 months

after renal transplantation. All patients were admitted to the 3rd Xiangya Hospital of Central South University, a large tertiary comprehensive hospital with 2200 beds. All patients underwent renal transplantation between January 2014 and October 2018. The transplanted organs were from either living donors or from donation after cardiac death (DCD). The living donors were all direct relatives of the recipients. All renal transplants were reviewed and approved by the Hospital Ethics Committee (HOC) and the Health and Family Planning Commission of Hunan Province, China. Organs from DCD were all approved by the China Organ Transplant Response System (COTRS). All transplant donors, or their next of kin, provided written informed consent, which was freely given. The protocol of our study was reviewed and approved by the Ethics Review Board of the 3rd Xiangya Hospital of Central South University, China.

The study inclusion criteria required that all the transplant recipients admitted to our hospital were diagnosed with pneumonia. The criteria for the diagnosis of pneumonia were based on the Centers for Disease Control and Prevention (CDC) criteria, and included symptoms of fever, cough, sputum production, chest pain, shortness of breath, and respiratory failure, with new-onset or progression of lung infiltrates on chest radiography or computed tomography (CT). The exclusion criteria of our study included age <18 years, onset of pneumonia more than 6 months after transplantation, serum creatinine on hospital admission of >3 mg/dL, loss to follow-up, history of recent blood transfusion, acute bleeding, hematologic diseases, or recipients of multiorgan transplants. A standardized immunosuppressive regimen for all kidney transplant recipients included was maintained with tacrolimus (0.1 mg/kg administered every 12 h, tacrolimus valley point concentrations: 6~8 ng/mL), mycophenolate mofetil (500 mg twice daily), and prednisolone (maintenance dose, 5~10 mg). All immunosuppressants were discontinued at ICU admission, and methylprednisolone (1 mg/kg every 12 h) was initiated, followed by a gradual tapering. Empirical antibiotic therapy included teicoplanin, meropenem, ganciclovir, and trimethoprim/sulfamethoxazole (TMP-SMX). An antifungal drug was administered in cases with suspected or confirmed fungal infection.

Definitions of bacteremia and red blood cell distribution width (RDW)

Significant bacteremia was diagnosed by culturing the blood for bacteria and by clinical symptoms of fever and sepsis. The criteria at our center for intensive care unit (ICU) admission referred to the 2007 Infectious Disease Society of America (IDSA) and the American Thoracic Society (ATS) guidelines for severe community-acquired pneumonia for admission to the ICU [21]. In our hospital, the upper limit of the reference interval of the red blood cell distribution width (RDW) was 15.0%, and in this study the RDW was considered high at >15.0%.

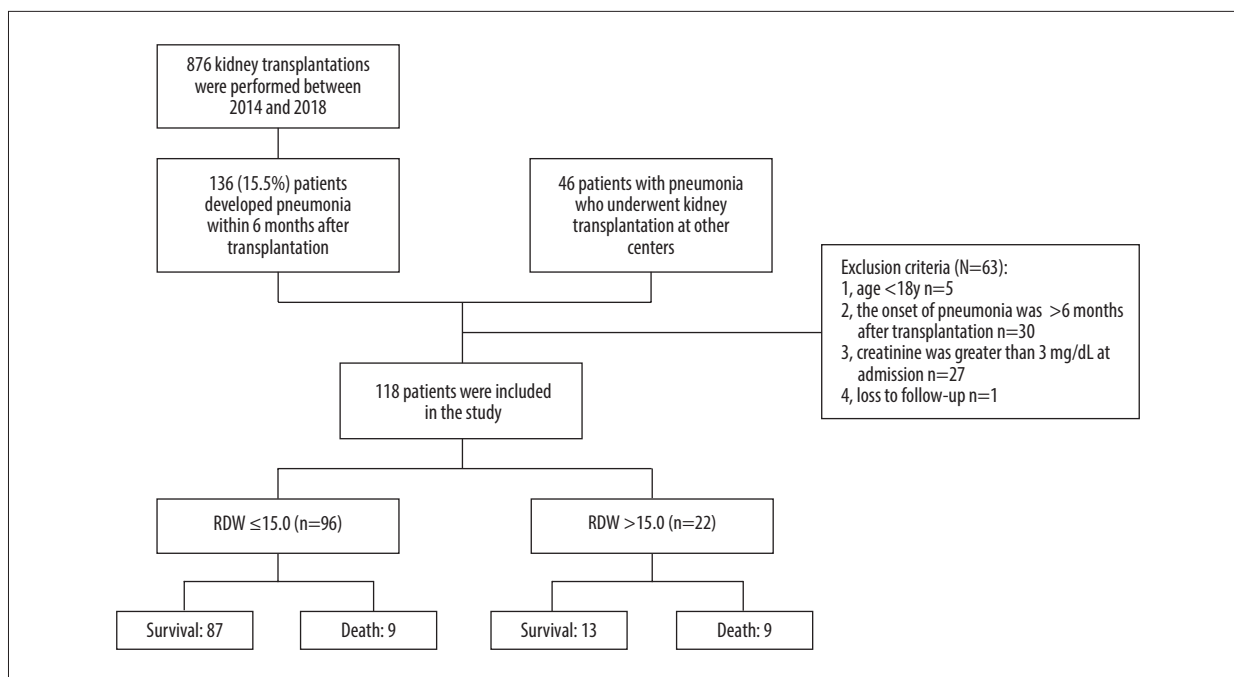


Figure 1. The flow diagram of the study cohort who underwent measurement of red blood cell distribution width (RDW).

Laboratory measurements

Blood samples from renal transplant recipients with early-onset pneumonia were collected when pneumonia was diagnosed. Blood culture tests were performed by the Department of Laboratory Medicine of the 3rd Xiangya Hospital of the Central South University in Hunan Province, China. The hematological indices analyzed included hemoglobin, neutrophil count, lymphocyte count, platelet count, and red cell distribution width (RDW). The blood samples were collected in EDTA-K2 tubes (Becton-Dickinson, Franklin Lakes, NJ, USA) and examined for blood parameters with the CAL 8000 New Generation Cellular Analyzer (Mindray, Shenzhen, China).

Statistical analysis

Statistical analysis was performed using SPSS version 19.0 (SPSS, Chicago, IL, USA). Continuous variables were compared by *t* test, and described as mean±standard deviation (SD). Categorical variables were depicted as a frequency or percentage and examined through the chi-square test or Fisher's exact test. The patients were categorized into 2 groups by RDW, with RDW ≤15.0% (n=96) and RDW >15.0% (n=22), which were compared. The 60-day mortality, bacteremia, requirement for mechanical ventilation, graft rejection, and ICU admission were compared by Kaplan-Meier method. Cox univariate regression analysis was performed to identify prognostic variables for mortality, and variables with *P*<0.1 were analyzed to identify independent variables using Cox multivariate regression analysis. The results were expressed as the hazard ratio (HR)

and 95% confidence interval (CI). *P*<0.05 was regarded as a significant difference.

Results

Study population

A flow diagram of the study is shown in Figure 1. There were 876 patients who received renal transplantation from 2014 to 2018 in our hospital, and 181 patients who developed early-onset pneumonia. There were 63 patients who were excluded because their age was <18 years (n=5), the onset of pneumonia was >6 months after transplantation (n=30), the plasma creatinine was >3 mg/dL on admission (n=27), or they were lost to follow-up (n=1). There were 118 kidney transplant recipients with early-onset pneumonia included in this study cohort, and 22 patients had increased red blood cell distribution width (RDW) >15.0%. There were 9 postoperative deaths.

Characteristics of the study population

Baseline characteristics of the kidney transplant recipients included in the study were stratified according to the RDW levels and are presented in Table 1. After applying inclusion and exclusion criteria, 118 patients were enrolled in our study. The mean age was 41.53±9.97 years, 84 (71.2%) were male, and 18 patients (15.3%) died in the follow-up period (Table 1). The RDW ranged from 11.8% to 18.4%, and 22 patients had RDW values higher than the upper normal limit (RDW >15.0%).

Table 1. Baseline characteristics of the patients, including red blood cell distribution width (RDW).

	Total (n=118)	RDW ≤15.0 (n=96)	RDW >15.0 (n=22)	P
Age (years)	41.53±9.97	40.71±9.31	45.09±12.02	0.12
Male (%)	84 (71.2%)	68 (70.8%)	16 (72.7%)	0.86
DCD (%)	105 (89.0%)	85 (88.5%)	20 (90.9%)	0.749
The time after transplantation (months)	110.41±64.13	118.02±65.24	77.18±47.26	0.007
Diabetes (%)	10 (8.47%)	8 (8.33%)	2 (9.09%)	0.908
Cr admission (μmol/L)	159.96±74.09	154.74±58.51	182.73±93.19	0.11
BUN (mmol/L)	12.23±7.41	11.11±5.57	17.11±11.61	0.027
Albumin (g/L)	36.89±4.99	37.34±4.73	34.92±5.69	0.04
PCT (μg/L)	0.56±1.09	0.35±0.49	1.46±2.13	0.024
CRP (mg/L)	51.28±57.14	44.53±44.13	80.70±90.94	0.082
ESR (mm/h)	40.25±25.68	38.26±23.96	48.91±31.31	0.079
L (10 ⁹ /L)	0.80±0.50	0.82±0.50	0.70±0.51	0.329
N (10 ⁹ /L)	7.32±4.27	7.28±4.31	7.46±4.15	0.861
WBC (10 ⁹ /L)	8.83±4.59	8.86±4.63	8.72±4.52	0.9
Hb (g/L)	110.27±21.89	113.38±19.95	96.73±25.17	0.001
Hct (%)	34.30±6.68	35.18±6.10	30.44±7.81	0.002
NLR	12.35±11.20	11.24±8.58	30.45±7.81	0.15

DCD – donation after citizen’s death; PCT – procalcitonin; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; L – lymphocyte; N – neutrophil; Hb – hemoglobin; Hct – hematocrit; NLR – neutrophil-lymphocyte ratio.

The group with high RDW had a significantly shorter recovery time after transplantation, and a lower serum albumin, hemoglobin (Hb), and hematocrit (Hct), with higher blood urea nitrogen (BUN) and procalcitonin (PCT) ($P<0.05$) (Table 1). There were no significant differences in age, donation after cardiac death (DCD), diabetes, serum creatinine at admission, lymphocyte (L), neutrophil (N), white blood cell (WBC) count, neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), or erythrocyte sedimentation rate (ESR).

RDW and prognosis

In this study, 18 patients died, and the 60-day death rate was 15.3% (18/118). The group with increased RDW had a much higher risk of death than the group with a standard RDW (40.9% vs. 9.38%; $P<0.001$), which showed statistically significant differences according to the Kaplan-Meier method (Table 2, Figure 2). Increased RDW was significantly associated with an increase in mechanical ventilation (50.0% vs. 13.5%) ($P<0.01$), ICU length of stay (45.5% vs. 9.38%) ($P<0.01$), and renal transplant rejection (18.2% vs. 2.08%) ($P<0.01$). No significant difference was

shown in bacteremia between the 2 study groups ($P=0.07$) (Table 2, Figure 2).

Univariate Cox regression analysis showed that age (HR, 1.084; 95% CI, 1.001–1.098; $P=0.045$), BUN (HR, 1.045; 95% CI, 1.005–1.086; $P=0.027$), albumin (HR, 0.866; 95% CI, 0.788–0.952; $P=0.003$), lymphocyte count (HR, 0.208; 95% CI, 0.052–0.840; $P=0.027$), Hb (HR, 0.968; 95% CI, 0.946–0.991; $P=0.06$), Hct (HR, 0.897; 95% CI, 0.832–0.966; $P=0.020$), and RDW (HR, 1.637; 95% CI, 1.222–2.193; $P=0.001$) were independent predictors for 60-day mortality (Table 3). Multivariate Cox proportional hazard analysis demonstrated that serum albumin (HR, 0.884; 95% CI, 0.796–0.981; $P=0.020$) and RDW (HR, 1.672; 95% CI, 1.111–2.516; $P=0.014$) were independent prognostic factors (Table 3).

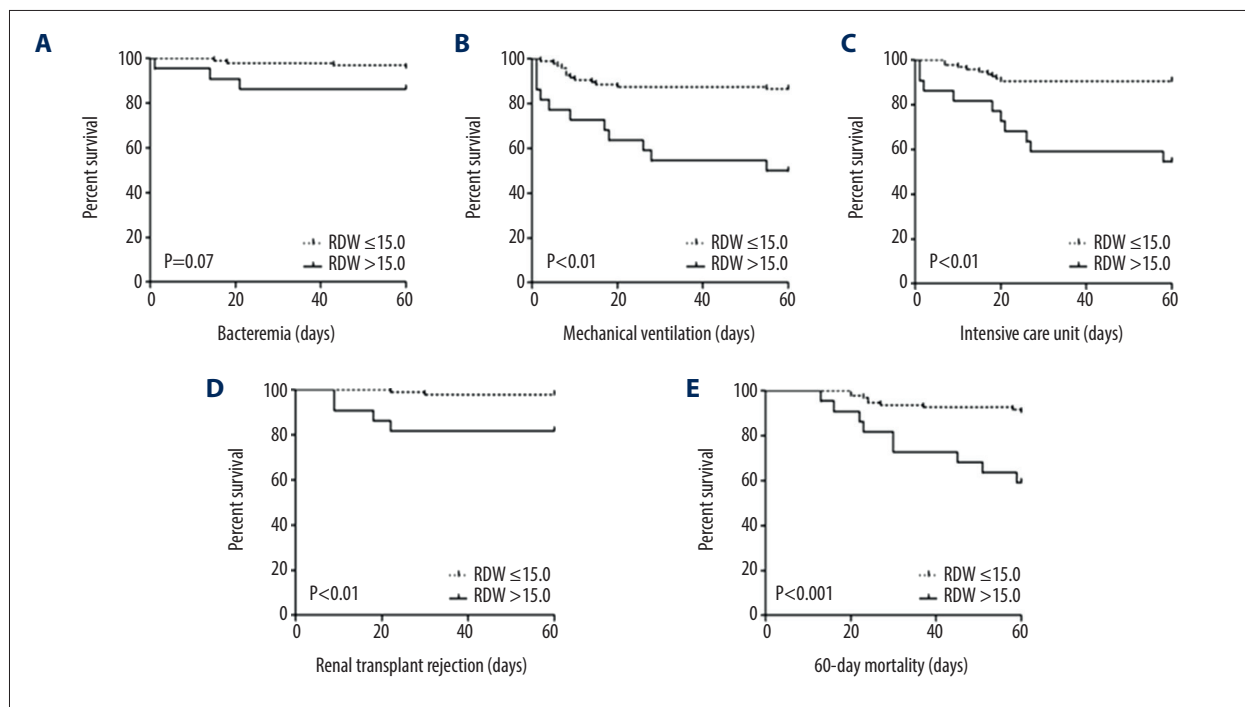
Discussion

Pneumonia is a leading cause of death early after kidney transplant. With the recent application of donation after cardiac

Table 2. Patient prognosis by red blood cell distribution width (RDW).

	RDW ≤ 15.0 (n=96)	RDW > 15.0 (n=22)	P
Bacteremia (%)	4.17% (4)	13.6% (3)	0.07
Mechanical ventilation (%)	13.5% (13)	50.0% (11)	<0.01
ICU (%)	9.38% (9)	45.5% (10)	<0.01
Renal transplant rejection (%)	2.08% (2)	18.2% (4)	<0.01
Mortality(%)	9.38% (9)	40.9% (9)	<0.001

ICU – Intensive Care Unit.

**Figure 2.** Kaplan-Meier survival curve of the groups with a red blood cell distribution width (RDW) of $\leq 15.0\%$ and $> 15.0\%$ according to the log-rank test. (A) Kaplan-Meier survival curve for bacteremia ($P=0.07$); (B) Kaplan-Meier survival curve for mechanical ventilation ($P<0.01$); (C) Kaplan-Meier survival curve for stay in the Intensive Care Unit (ICU) ($P<0.01$); (D) Kaplan-Meier survival curve for transplant rejection ($P<0.01$); (E) Kaplan-Meier survival curve for 60-day mortality ($P<0.001$).

death (DCD) for renal transplantation in China, the transplant recipients will be more susceptible to donor-related infection and will receive more potent immunosuppression treatment, which leads to an increased incidence of pneumonia. The present study showed a high rate of infection-related mortality (15.3%) among renal transplant recipients with early-onset pneumonia in our center. The death rate in this study was consistent with the findings from a previous study, which indicated a mortality rate of 10–30% in renal transplant recipients with pneumonia [3].

Our study showed that an increased red blood cell distribution width (RDW) in kidney transplant recipients with early-onset pneumonia was related to increased patient mortality.

An increased RDW was significantly associated with the severity of bacteremia, the requirement for mechanical ventilation, ICU length of stay, and renal transplant rejection, and was an independent predictive index for 60-day mortality among renal graft recipients with pneumonia. Also, patients with lower albumin had a higher mortality rate.

The RDW has previously been demonstrated to be a diagnostic marker for anemia, and is a reliable marker for cardiovascular disease and malignancy [9,16,22]. Recently, RDW has been suggested to be an independent predictor in inflammatory and infectious diseases [17,18,20]. Recently, Ku et al. showed that RDW was an independent predictor of death among patients with gram-negative bacteremia [18]. Community-acquired

Table 3. Cox proportional hazards regression analysis for 60-day mortality associated with red blood cell distribution width (RDW).

	Univariate HR (95% CI)		P	Multivariate HR (95% CI)		P
Age	1.048	(1.001~1.098)	0.045	1.001	(0.954~1.051)	0.955
Male	0.815	(0.306~2.171)	0.682			
DCD	0.610	(0.176~2.106)	0.434			
The time after transplantation	1.003	(0.997~1.010)	0.347			
Diabetes	1.501	(0.345~6.529)	0.588			
Cr admission	1.003	(0.998~1.007)	0.232			
BUN	1.045	(1.005~1.086)	0.027	0.942	(0.879~1.010)	0.092
Albumin	0.866	(0.788~0.952)	0.003	0.884	(0.796~0.981)	0.020
PCT	1.073	(0.744~1.546)	0.707			
CRP	1.005	(0.999~1.010)	0.127			
ESR	1.004	(0.987~1.022)	0.623			
L	0.208	(0.052~0.840)	0.027	0.295	(0.074~1.174)	0.083
N	0.924	(0.812~1.051)	0.228			
WBC	0.910	(0.804~1.029)	0.131			
Hb	0.968	(0.946~0.991)	0.06	1.094	(0.939~1.276)	0.249
Hct	0.897	(0.832~0.966)	0.004	0.707	(0.424~1.180)	0.185
RDW	1.637	(1.222~2.193)	0.001	1.672	(1.111~2.516)	0.014
NLR	1.013	(0.981~1.047)	0.424			

DCD – donation after citizen’s death; PCT – procalcitonin; CRP – C-reactive protein; ESR – erythrocyte sedimentation rate; L – lymphocyte; N – neutrophil; Hb – hemoglobin; Hct – hematocrit; NLR – neutrophil-lymphocyte ratio.

pneumonia and severe sepsis have also recently been shown to be associated with increased RDW [19].

Although the underlying mechanisms by which RDW is associated with mortality remain unclear, previous studies have identified several plausible explanations. Systemic inflammation has been suggested to predict disease progression and mortality from cardiovascular disease in patients in the ICU. Systemic inflammation is present in early-onset pneumonia in kidney transplant recipients, and inflammation has been shown to affect bone marrow function and iron metabolism [23]. Also, pro-inflammatory factors, including tumor necrosis factor- α (TNF- α), interleukin-6 (IL-6), and interleukin-1 β (IL-1 β), have been shown to inhibit erythrocyte maturation and to reduce the life span of red blood cells (RBCs), resulting in increases RDW [24]. Oxidative stress may be a contributing factor in the association between RDW and mortality [25]. Pneumonia patients experience severe oxidative stress due to neutrophil activation, and oxidative stress has been proposed to increase RDW by reducing the survival of RBCs and enhancing the release of large immature RBCs into the circulation [18]. Reduced levels of anti-oxidants are also associated with increased RDW values. Another explanation may be related to malnutrition,

which is common in patients with pneumonia. In the present study, albumin was also an independent risk factor for 60-day mortality, which reflects nutritional status. Therefore, there are several lines of evidence supporting that RDW is a promising indicator of the complex association between malnutrition and inflammation [26]. RDW is also thought to be closely related to reduced renal function [27,28]. In renal transplant recipients, impaired renal function occurs for many reasons, including chronic rejection and immunosuppressive therapy.

There are several limitations in this study. It was a single-center retrospective study with a small sample size. The data analyzed were dependent on the accuracy and availability of the medical records. The use of a single center may have introduced bias into the data collection or analysis. However, this study is the first to show the association between increased RDW in renal transplant recipients with early-onset pneumonia. Further prospective, controlled, large-scale, multicenter studies should be performed to confirm the prognostic role of high RDW and patient outcome following kidney transplantation.

Conclusions

We explored the significance of red blood cell distribution width (RDW) in predicting prognosis, including 60-day mortality, in renal transplant recipients with early-onset pneumonia. RDW was significantly associated with the severity of early-onset pneumonia and 60-day mortality in renal transplant recipients.

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Further studies are required to explore the mechanism for the association between RDW values and mortality among kidney transplant recipients with early-onset pneumonia.

Conflict of interest

None.