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The clinical significance of neutrophil-lymphocyte ratio in patients treated with hemodialysis complicated with lung infection

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Abstract

The goal of this work was to investigate the potential significance of neutrophil-lymphocyte ratio (NLR) in patients treated with maintenance hemodialysis (MHD).

Herein, we retrospectively reviewed the electronic medical records of 100 patients with end-stage renal failure who were treated with MHD. All patients enrolled in this study met the inclusion criteria and were followed. The differences in each indicator between the two groups were compared using the Wilcoxon rank-sum test. On the other hand, Spearman correlation and logistic regression analysis were used to explore the correlation and risk factors for pulmonary infection between NLR and other indicators. Finally, we determined the optimal cut-off values for NLR, hypersensitive c-reactive protein (hs-CRP), and procalcitonin (PCT) diagnosis of pulmonary infection using the receiver operating characteristic curve.

We found that NLR was positively correlated with age, PCT, hs-CRP, and hospital stay, but negatively correlated with hemoglobin, red blood cell, and Albumin. The expression levels of PCT, hs-CRP, and NLR in the infected group decreased significantly than those before treatment. Multiple regression analysis revealed that NLR is an important independent risk factor for MHD patients with pulmonary infection. Additionally, receiver operating characteristic curve analysis showed that the sensitivity, specificity, and area under the curve were 87.76%, 100%, and 0.920 when using NLR combined with hs-CRP to predict pulmonary infection in MHD patients, whereas that of NLR combined with PCT were 87.76%, 96.08%, and 0.944, respectively.

Findings from this study suggested that NLR is an independent risk factor for MHD patients with pulmonary infection, which can effectively predict pulmonary infection. Moreover, sensitivity and specificity were greatly enhanced when using NLR combined with PCT/hs-CRP to predict pulmonary infection in MHD patients.

Abbreviations: Alb = Albumin, AUC = area under the curve, AVF = arteriovenous fistula, BMI = body mass index, CAP = community-acquired pneumonia, CKD = chronic kidney disease, ESRD = end-stage renal disease, Hb = hemoglobin, HD = hemodialysis, hs-CRP = hypersensitive c-reactive protein, IL-6 = interleukin-6, LYM = lymphocyte, MHD = maintenance hemodialysis, NLR = neutrophil/lymphocyte ratio, PCT = procalcitonin, RBC = red blood cell, TNF-α = tumour necrosis factor, WBC = white blood cell.

Keywords: end-stage renal disease, lung infection, maintenance hemodialysis, neutrophil/lymphocyte ratio

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1. Introduction

Chronic kidney disease (CKD) is an irreversible disease, characterized by abnormal renal structure/function for three or more months. Typically, CKD patients detected renal damage markers (albuminuria, tubular-associated lesions, histological and imaging abnormalities) or had a history of renal transplantation with or without a decrease in glomerular filtration rate (GFR), or GFR < 60 ml/ (min·1.73^2) ≥ 3 months.[1] When this disease progresses to end-stage renal disease (ESRD) GFR < 15 ml/min, this implies that renal function is no longer viable and thus requires renal replacement therapy. According to the 2019 U.S. kidney data system report, the incidence of CKD in the U.S. was about 14.5% in 2017, while the number of ESRD was approximately 747000, indicating an annual increasing trend.[2] Moreover, a study published in Lancet in 2012 showed[3] that the prevalence of CKD in China was roughly 10.8% while the total number of CKD was about 120 million.

Globally, among the most common treatments for ESRD patients includes hemodialysis, peritoneal dialysis, and kidney transplantation, of which hemodialysis (HD) remains the most important strategy. Hemodialysis involves the extracorporeal circulation of the patient's blood coupled with diffusion, convection, and adsorption principles to effectively remove excess water and toxins in the body of patients with renal failure, thus correcting water, electrolyte, and acid-base disorders.[4–7] Recently, with the continuous improvement of blood purification technology, maintenance hemodialysis (MHD) has gradually enhanced as well as prolonged the quality of life and longevity of ESRD patients. However, its long-term complications remain the key challenge affecting its efficacy. In practice, MHD aims to partially replace the detoxification and metabolic function of the kidney, but still can not completely correct the metabolic disorder state of ESRD patients, eventually leading to infection with various diseases such as cardiovascular and cerebrovascular diseases, malnutrition, anemia, and other complications.[8–11]

As one of the major complications of MHD patients, infection is the second major cause that affects the prognosis of dialysis patients and leads to their death. Infection particularly pulmonary infections in dialysis patients are common in clinical practice. For instance, about 1/4 of the infections can be attributed to pulmonary factors.[9,12–14] The mortality rate of pulmonary infection in HD patients has been estimated to be 15 times higher than that in the general population, of which 1/5 of patients can develop pneumonia within 1 year after starting dialysis treatment.[12] Related studies have found[15,16] that infection-related hospital risk factors mainly include age (the older the age, the greater the risk), sex (the greater the risk for women), history of diabetes, heart failure, lung disease, and low serum albumin (Alb). In the past few years, it has been uncovered that in addition to the above traditional risk factors, the continuous microinflammatory state of ESRD patients may play a key role in the occurrence and development of pulmonary infection.[17,18] For this reason, the prognosis of MHD patients is positive if the risk factors of pulmonary infection are identified and given early intervention.

Mounting evidence shows that the neutrophil-to-lymphocyte ratio (NLR) is closely related to the inflammatory response in the body, and its value as a biomarker is indispensable.[19–21] In addition, NLR is obtained by dividing the neutrophil count by lymphocyte (LYM) count, which makes it an economical and simple parameter that can easily assess the inflammatory state of the body.[21] Multiple studies have noted that elevated NLR can effectively reflect the microinflammatory state of MHD patients and can also be used as important predictors of cardiovascular disease, multiple tumor outcomes, vascular calcification, and all-cause mortality.[19,20,22–24]

NLR comprises of two leukocyte subtypes, neutrophils, and LYM. Numerous recent studies have found a significant correlation between NLR with classical inflammatory indicators, such as interleukin 6 (IL-6), hypersensitive C reactive protein (hs-CRP), and tumor necrosis factor α (TNF-α), as well as inflammation and immune dysfunction.[21,25] Elsewhere, relevant studies have identified that NLR is closely associated with community-acquired pneumonia (CAP) and can be used as an effective indicator to assist in the diagnosis of CAP and to judge prognosis.[26,27] However, there is a paucity of information in the current study between NLR and MHD patients with pulmonary infection. Therefore, in this context, this study preliminarily explored the potential association between NLR and pulmonary infection in peripheral blood and its predictive value for pulmonary infection in MHD patients.

2. Methodology

In the present study, we retrospectively collected clinical data of 100 MHD patients and eventually performed the statistical analysis to explore the potential value of peripheral blood NLR in pulmonary infection in MHD patients.

3. Sample size

In this study, 100 adult patients with end-stage renal failure who were treated with MHD at the purification center of the Department of Renal Medicine blood, the first affiliated hospital of Kunming Medical University from March 1, 2017, to February 28, 2019, were enrolled as study subjects. Their medical records were followed up for at least one year (the follow-up deadline was February 29, 2020). The patients comprised of 67 males (67%), 33 females (33%), and average age (52.3 ± 16.6).

4. Patient recruitment criteria

4.1. Inclusion criteria

Eligibility criteria for enrollment in this work were as follows: adult patients (age ≥ 18 years) diagnosed with CKD5 stage and given routine MHD treatment with dialysis for not less than 3 months, new lung infections that meet CAP or healthcare-related pneumonia diagnostic criteria, specifically selected about 50:50 patients with / without pulmonary infection.

4.2. Exclusion criteria

Exclusions included other infections such as those associated with the hemodialysis pathway, infections of the digestive and urinary systems. In addition, patients under 18 years after kidney transplantation, with long-term use of hormones and associated immunosuppressants, with severe heart failure, malignant tumor, pregnancy, mental illness, tuberculosis, with recent surgical treatment and with incomplete/missing clinical data.

4.3. Diagnostic criteria for uremia pneumonia

Uremia diagnosis is defined as the diagnostic criteria of the 2012 KDIGO clinical practice guidelines.[28] CAP diagnosis refers to

the guidelines for the diagnosis and treatment of adult CAP in China developed by the Respiratory Society of the Chinese Medical Association in 2016,[29] while health care-associated pneumonia diagnosis is a clinical diagnosis that is based on the guidelines for the diagnosis of healthcare-related pneumonia developed by the American Chest Science Association and the American Infectious Disease Society (ATS/IDSA) in 2005,[30] which is integrated with the patient's related clinical symptoms, laboratory test indicators, imaging, and etiological test results. MHD pulmonary infection patients received anti-infection and symptomatic support treatment. The reexamination timing of patients was that the patient's condition was significantly improved after being given active treatment or met the discharge criteria.

The basis for the clinical diagnosis of pneumonia was as follows: (1) X-ray film showing patchy infiltration, consolidation of leaves or segments, glazing-like shadows, or interstitial changes. (2) At least one of the following symptoms: a. Recently appeared cough and expectoration with purulent sputum, b. Fever, body temperature > 38.0°C, c. May hear moist rales or signs of pulmonary consolidation, d. Peripheral blood leukocyte count $> 10 \times 10^9$/L or $< 4 \times 10^9$/L.

5. Procedure

5.1. Patient recruitment

Patients undergoing hemodialysis were contacted and the purpose of the study explained to them. Those patients who were willing to participate signed a written informed consent form.

5.2. General collection

The clinical data of MHD patients treated at the blood purification center of our hospital were collected. This included:

(1) Basic information: name, sex, age, height, weight, and smoking history.
(2) Primary disease composition: Diabetic end-stage nephropathy, chronic glomerulonephritis, hypertensive nephropathy, lupus nephropathy, polycystic kidney disease, and unexplained renal failure.
(3) Associated complications: Hypertension, coronary heart disease, and arteriosclerosis.
(4) Dialysis related factors: Start dialysis time, dialysis mode, duration of dialysis, and weekly dialysis frequency.
(5) Other related information: Length of hospital stay and the number of acute exacerbations within 1 year after discharge from the infection group.
(6) Timing of blood sampling: Non-infection group; the next morning after admission to the hospital to extract blood before dialysis, infection group: before dialysis to extract the patient's fever, shivering blood, infected patients after treatment improved, and then extract the next morning before dialysis blood, and then calculate its NLR value.

5.3. Testing indicators

We used the hospital electronic medical record management system to obtain MHD patients related laboratory data before dialysis including blood routine (8 indicators), such as (white blood cell [WBC], red blood cell (RBC), hemoglobin (Hb), NEU, LYM, PLT, among others) and blood biochemistry (23 indicators), namely (Alb, hs-CRP, procalcitonin (PCT), Cr, blood urea nitrogen, Ca, P, Fe, intact parathyroid hormone, 25OH-VitD, TC, triglyceride, among others). Subsequently, we also recorded data on the infection of blood culture, sputum culture, and re-examination of blood routine after the improvement of treatment mainly for NEU and LYM. The phlegm culture etiology results and imaging data primarily included chest X-ray or CT. The above examination results and imaging examination were completed independently by our laboratory and imaging department. We computed the values of NLR of the infected group before treatment and after treatment (the ratio of NEU to LYM count) and body mass index (weight (kg)/height^2(m)). Finally, the estimated glomerular filtration rate was calculated by the modification of diet in renal disease equation as follows: estimated glomerular filtration rate (ml/min·1.73^2) = 175 (Scr) mg/l$^{-1.154} \times$ age$^{-0.203}$(0.742 female).

6. Research methods

6.1. Grouping

Here, we classified 100 MHD patients based on the following methods: 1) According to whether the patients were accompanied by a lung infection, where they were divided into an infected group or a non-infected group. The two groups were composed as follows: infection group 49 (34 males, 15 females, mean age 54.0 ± 17.1) and non-infection group 51 (33 males, 18 females, mean age 50.7 ± 16.1). 2) Further, we divided the infection group into two subgroups: low NLR (NLR ≤ 6.6) and high NLR (NLR > 6.6) groups according to the median of NLR.

6.2. Dialysis mode

All ESRD patients were treated regularly by hemodialysis on a polysulfone membrane dialyzer with bicarbonate as dialysate. Based on the different coagulation function of the patients, they were given low molecular weight heparin or common heparin anticoagulant, or even without heparin dialysis in special cases. The dialysate flow rate was 500 ml/min in all sessions, while the blood flow rate was about 200 to 300 ml/min. Dialysis frequency was 4 h/t, 2 to 3 times/wk.

7. Ethical considerations

This study was approved by the First Affiliated Hospital of Kunming Medical University Ethics Committee (Approval No:174296). All patients provided written informed consent. The names and identities of the respondents were kept completely anonymous.

8. Statistical analysis

Statistical data analysis was performed using SPSS, version 23.0 for Windows 10 (SPSS Inc., Chicago, IL). Continuous variable data that conforms to the normal distribution are presented as ($\overline{x} \pm s$). The comparison between groups was tested using the independent sample *t*-test. On the other hand, measurement data that did not conform to the normal distribution are expressed as the median (25th and 75th percentile), where the Wilcoxon rank-sum test was used for comparison between groups. Furthermore,

Table 1

Comparison of clinical data between infected and noninfected groups.

Category	Total	Non-infected group	Infected group	χ^2/z	*P* value
Day in hospital	14.5 (10.0–19.8)	7.0 (6.0–10.0)	15 (10–19.5)	–6.196[c]	<.001[*]
BMI (Kg/m2)	22.6 (20.0–25.3)	23.0 (20.7–25.5)	21.6 (19.8–25.3)	–1.15[c]	.251
Heart rate (beats/min)	83 (75–92)	80 (72–85)	90 (80–102)	–4.295[c]	<.001[*]
Dialysis per wk (n[%])				3.28[a]	.07
≤2 times	48[48]	29[57]	19[39]		
>2 times	52[52]	22[43]	30[61]		

BMI = body mass index.

[a] χ2 value.

[c] z value; Patients were defined as treated with maintenance hemodialysis.

[*] A *P* of <.05 represents significant variance between the groups.

percentages (%) were used for counting data, χ2 was used to compare between groups, and the Spearman correlation test was used to explore the association between NLR and other indicators. Finally, the logistic regression analysis was implemented to analyze the risk factors of lung infection, while the receiver operating characteristic curve (ROC) was used to evaluate the predictive value of NLR combined with hs-CPR and PCT on pulmonary infection in MHD patients. A level of $P < .05$ was considered statistically significant.

9. Results

9.1. Demographic characteristics

The patients with drinking history in the infected group were higher than those in the control group (Table S1, Supplemental Digital Content, http://links.lww.com/MD/G249). Among the 49 infected patients, 21 (43%) had diabetic nephropathy, 17 (35%) chronic glomerulonephritis, 3 (6%) hyperplastic IgA nephropathy, 2 (4%) lupus nephritis, and 1 (2%) hypertensive nephropathy (Table S2, Supplemental Digital Content, http://links.lww.com/MD/G250). The most prevalent pathogenic bacteria were gram-negative bacteria, in which the detection rate was 34.7%. Among them, 11 strains of G- bacteria accounted for 64.7%, mainly *Klebsiella pneumoniae* infection, 2 strains of G bacteria accounting for 11.8%, and 4 strains of fungi accounting for 23.5% (Table S3, Supplemental Digital Content, http://links.lww.com/MD/G251). Among the patients with diabetic nephropathy, the highest detection rate of pathogenic bacteria was 13 cases, in which the detection rate was 28.9% with G- as the main factor (Table S4, Supplemental Digital Content, http://links.lww.com/MD/G252). Based on the χ^2 test results, the number of days in the hospital and heart rate in the infected group was significantly higher than that in the non-infected group (Table 1). Nonparametric rank test analysis revealed that the expression level of NLR, WBC, NEU, PCT, hs-CRP, and triglyceride in the infected group was considerably higher compared to that in the non-infected group, while the levels of RBC, Hb, LYM, and Alb expression were lower (Table 2, Fig. 1A).

9.2. Single-factor and multivariate logistic analysis screening risk factors for pulmonary infection in MHD patients

Univariate logistic regression analysis showed that alcohol consumption, Hb, RBC, WBC, NEU, LYM, NLR, Alb, PCT, and hs-CRP were the primary factors affecting MHD patients complicated with pulmonary infection. In addition, drinking, WBC, NEU, NLR, PCT, and hs-CRP were the risk factors leading to pulmonary infection in MHD patients, while Hb, RBC, LYM, and Alb were the protective factors (Table 3). We used multivariate logistic regression analysis to test the data that was significant in univariate logistic regression. Our findings demonstrated that Model 1: PCT (OR = 3.68, 95% CI = 1.02 – 13.24) and hs-CRP (OR = 1.67, 95% CI = 1.05 – 2.64) were independent risk factors for MHD concurrent pulmonary infections, while blood LYM (OR = 0.02, 95% CI = 0.00 - 0.35) was its independent protective factor. Model 2 results showed that for every 1 NLR (OR = 1.46, 95% CI = 1.14 - 1.86) increase, the risk of lung infection increased by 46% (Table 4).

9.3. Analysis of correlation index and NLR relation in the infected group after treatment

Nonparametric rank test analysis findings showed that the HR, PCT, CRP, and NLR levels of the infected group after anti-infection treatment were significantly lower compared to that before treatment (Table 5). The results of univariate logistic regression analysis indicated that WBC, PCT, and hs-CRP were important risk factors, whereas Hb, RBC, and Alb were protective factors (Table 6).

9.4. Correlation analysis of NLR and clinical indicators

The findings of the Spearman correlation analysis showed that positive correlations between NLR level with age, PCT, and hs-CRP were r = 0.249, 0.466, and 0.432, while its negative correlation values with Hb, RBC, and Alb were r = -0.372, -0.379, and -0.318, respectively, so showing a weaker association strength (Fig. 1B-G). Additionally, patients were divided into low NLR (NLR < 4.19) and high NLR (NLR ≥ 4.19) groups. Notably, nonparametric rank test analysis revealed that the larger the NLR, the longer the hospitalization time of dialysis patients. The positive correlation value between NLR and length of hospital stay was r = 0.388 (Table 7, Fig. 1H).

9.5. Using ROC curve to evaluate the diagnostic efficacy of NLR, hs-CRP, PCT, and NLR combined with hs-CRP/PCT

The results of the ROC analysis of the subjects showed that area under the curve (AUC) of CRP, PCT, NLR, NLR combined with CRP, and NLR combined with PCT for the diagnosis of pulmonary infection were 0.881 (95% CI 0.801 - 0.937), 0.95

Table 2

Comparison of laboratory indexes between infected and non-infected groups.

Category	Total population	Non-infected group	Infection group	t/z	*P value*
Hb (g/L)	97.6 ± 23.6	109.1 ± 23.0	85.1 ± 17.1	5.83[b]	<.001*
RBC (×10^{12}/L)	3.4 ± 0.8	3.9 ± 0.8	3.0 ± 0.6	6.37[b]	<.001*
WBC (×109/L)	7.0 (5.7–9.2)	6.1 (5.3–7.2)	8.7 (6.8–9.8)	−4.785[c]	<.001*
NEU (%)	72.0 ± 10.2	67.2 ± 8.4	77.2 ± 9.6	−5.44[b]	<.001*
NEU (×109/L)	4.5 (3.5–6.3)	4.1 (3.4–5.1)	5.7 (3.7–8.3)	−3.37[c]	.001*
LYM (%)	17.1 (12.8–22.6)	21.3 (17.1–25.0)	13 (9.1–15.8)	−5.55[c]	<.001*
LYM (×109/L)	1.1 (0.8–1.5)	1.3 (1.0–1.7)	0.9 (0.6–1.2)	−4.7[c]	<.001*
NLR	4.2 (3.0–6.7)	3.2 (2.7–4.1)	6.6 (4.2–11.6)	−5.66[c]	<.001*
PLT (×109/L)	195 (146.0–250.0)	200 (151.0–265.0)	185 (133.0–236.0)	−1.24[c]	.251
PT (s)	13.6 (13.2–14.0)	13.5 (13.2–13.8)	13.8 (13.2–14.4)	−1.54[c]	.124
APTT (s)	37.4 (36.0–40.7)	37 (35.6–39.2)	38.6 (36.0–42.0)	−1.87[c]	.061
FIB (g/L)	4.6 (3.8–5.5)	4.3 (3.7–5.1)	4.8 (4.0–5.7)	−1.29[c]	.198
Alb (g/L)	37.7 ± 6.3	40.6 ± 5.1	34.5 ± 5.9	5.49[b]	<.001*
TBIL (umol/L)	5.4 (4.1–7.1)	5.5 (4.6–7.0)	5.0 (3.5–7.2)	−0.98[c]	.327
DBIL (umol/L)	2.6 (2.0–3.2)	2.5 (2.0–3.2)	2.6 (2.0–3.4)	−0.34[c]	.733
IDIL (umol/L)	2.7 (2.1–3.9)	2.8 (2.3–4.1)	2.5 (1.3–3.7)	−1.83[c]	.068
BUN (mmol/L)	23.55 ± 8.1	24.9 ± 8.3	22.1 ± 7.7	1.82[b]	.072
Cr (umol/L)	802 (631.8–1036.3)	802 (671.0–1062.0)	802 (610.0–1030.0)	−0.63[c]	.526
PCT (ng/ml)	0.2 (0.1–1.4)	0.1 (0.1–0.1)	1.4 (0.8–3.4)	−7.86[c]	<.001*
hs-CRP (mg/L)	3.1 (3.0–22.1)	3.0 (3.0–3.0)	22.1 (7.4–63.8)	−6.69[c]	<.001*
IgG (g/L)	10.6 ± 3.0	11.0 ± 2.6	10.1 ± 3.3	1.56[b]	.122
IgM (g/L)	0.7 (0.5–0.8)	0.7 (0.5–0.9)	0.6 (0.5–0.7)	−1.59[c]	.112
IgA (g/L)	2.1 (1.8–2.8)	2.1 (1.8–2.5)	2.5 (1.7–2.8)	−1.19[c]	.235
C3 (g/L)	0.8 (0.8–1.0)	0.8 (0.8–1.0)	0.8 (0.8–1.0)	−0.59[c]	.555
C4 (g/L)	0.3 (0.2–0.3)	0.3 (0.2–0.3)	0.3 (0.2–0.3)	−0.3[c]	.767
25OH-VitD (ng/ml)	14.2 (9.0–19.7)	14.2 (11.4–23.0)	13.4 (6.6–18.2)	−1.76[c]	.079
Fe (umol/L)	9.4 (6.5–13.1)	10.1 (7.0–13.2)	8.8 (5.4–11.6)	−1.93[c]	.054
Ca (mmol/L)	2.1 (1.9–2.2)	2.1 (1.9–2.3)	2.0 (1.9–2.2)	−1.72[c]	.085
P (mmol/L)	1.9 (1.5–2.5)	1.9 (1.6–2.7)	1.9 (1.4–2.4)	−1.33[c]	.183
iPTH (pg/mL)	287.6 (189.1–369.6)	287.6 (198.0–342.2)	252.3 (183.2–452.5)	−0.61[c]	.541
TC (mmol/L)	3.5 (3.1–4.3)	3.7 (3.2–4.5)	3.4 (2.9–4.2)	−1.17[c]	.242
TG (mmol/L)	1.4 (1.1–2.0)	1.3 (1.0–1.9)	1.5 (1.1–2.2)	−2.07[c]	.039*
HDL-C (mmol/L)	1.0 (0.8–1.3)	1.0 (0.8–1.4)	1.0 (0.8–1.2)	−1.2[c]	.232
LDL-C (mmol/L)	2.0 (1.6–2.6)	2.1 (1.8–2.7)	1.9 (1.5–2.5)	−1.59[c]	.112
eGFR (ml/min/1.73^2)	5.73 (4.61–8.10)	5.71 (4.60–7.26)	5.93 (4.58–8.39)	0.446[c]	.762

APTT = activated coagulation time of whole blood, BUN = blood urea nitrogen, DBIL = direct bilirubin, eGFR = estimated glomerular filtration rate, HDL = high-density lipoprotein, IgG = immunoglobulin G, iPTH = intact parathyroid hormone, LDL = low-density lipoprotein, TG = triglyceride, WBC = white blood cell.

[b] t value.

[c] z value; Patients were defined as treated with maintenance hemodialysis.

* A *P* of <.05 represents significant variance between the groups.

NLR = neutrophil-lymphocyte ratio.

(95% CI 0.888–0.984), 0.829 (95% CI 0.740 - 0.897), 0.920 (95% CI 0.848 - 0.965), and 0.944 (95% CI 0.879 - 0.980), respectively. Consequently, the cut-off values were 3.23, 0.18, 5.52, 0.434, and 0.427, while that of sensitivity were 87.76%, 93.88%, 65.31%, 87.76%, and 87.76%, respectively. Finally, the specificity values were 96.08%, 88.24%, 94.12%, 100%, and 96.08%, respectively (Table 8, Fig. 1I).

10. Discussion

Pulmonary infection is the second most common cause affecting the quality of life and leading to death in MHD patients.[9,14,31] NLR can respond to both changes between inflammation and immune response simultaneously,[32] as well as exhibits a significant correlation with its classical inflammatory indicators, such as IL-6, TNF-α, and hs-CRP.[20,21,25] Besides, NLR consists of two different complementary immune pathways,[33] while inflammatory cytokines, such as IL-6 and TNF-α are primarily used in scientific research.[34] Interestingly, NLR values are easily obtained in the blood routine.

Elevated NLR is closely associated with the inflammatory state of the body.[35] As the severity of infection increases, so does the NLR.[36] It has been established that NLR, as an important predictor of cardiovascular disease in MHD patients,[37] can effectively reflect the inflammatory status of ESRD patients.[20] Moreover, NLR values are closely related to the severity of the pulmonary infection and clinical prognosis[38,39] as well as associated with erythropoietin (ESA) resistance, nutritional status and healthy prognosis, arteriovenous fistula stenosis, and renal tumor prognosis, among which the main factors can be attributed to chronic inflammation in MHD patients.[19,40–42]

10.1. Relationship between MHD and pulmonary infection

Long-term alcohol consumption may increase the chance of pulmonary infection after hemodialysis in ESRD patients. Red blood cells can regulate complement activity and enhance the

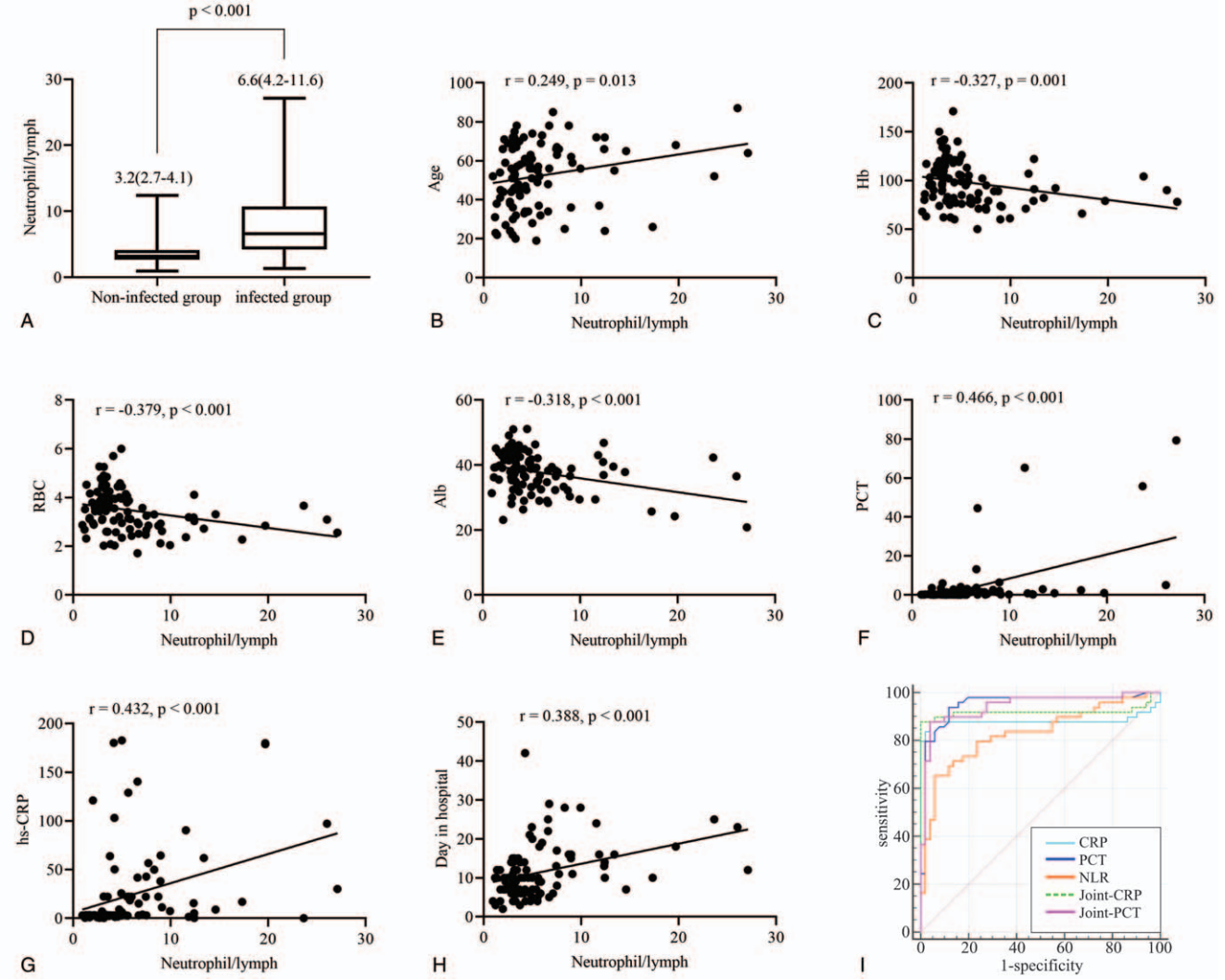

Figure 1. Relationship between neutral/lymphocyte ratio and clinical indicators in dialysis patients. A. Levels of NLR in infected and non-infected groups. Correlation between NLR and (B) age, (C) Hb, (D) RBC, (E) Alb, (F) PCT, (G) hs-CRP, and (H) length of hospital stay. (I) NLR, PCT, and CRP independent and combined projections of pulmonary infection ROC graph.

Table 3

Analysis of single factor logistic regression of pulmonary infection by indicators.

Category	B	OR	SE	95%CI	Wald	*P*-Value
Drink	1.02	2.77	0.51	1.02–7.56	3.98	.046
Hb	–0.06	0.94	0.01	0.92–0.97	20.04	<.001*
RBC	–1.48	0.23	0.34	0.12–0.44	18.91	<.001*
WBC	0.45	1.57	0.12	1.25–1.97	15.21	<.001*
NEU	0.39	1.48	0.12	1.17–1.86	10.95	.001*
LYM	–2.31	0.1	0.56	0.03–0.30	18.87	<.001*
NLR	0.53	1.69	0.13	1.31–2.18	16.51	<.001*
Alb	–0.21	0.81	0.05	0.74–0.90	18.3	<.001*
PCT	3.22	24.99	0.76	5.64–110.77	17.96	<.001*
hs-CRP	0.45	1.58	0.15	1.17–2.13	8.78	.003*

Patients were defined as treated with maintenance hemodialysis.

Alb = albumin, hs-CRP = hypersensitive c-reactive protein, PCT = procalcitonin, RBC = red blood cell, WBC = white blood cell.

* A *P* of <.05 represents significant variance between the groups.

NLR = neutrophil-lymphocyte ratio.

Table 4

Multiple factor logistic regression analysis of pulmonary infection by indicators.

	Model 1				Model 2			
Category	**OR**	**95%CI**	**Wald**	***P*-value**	**OR**	**95%CI**	**Wald**	***P*-value**
Drink	0.79	0.04–14.11	0.03	.87	–	–	–	–
Hb	1.08	0.96–1.22	1.62	.20	0.96	0.93–1.00	5.22	.02*
RBC	0.08	0.00–2.93	1.88	.17	–	–	–	–
WBC	2.00	0.50–8.06	0.95	.33	1.22	0.92–1.62	1.87	.171
NEU	0.42	0.09–1.93	1.25	.26	–	–	–	–
LYM	0.02	0.00–0.35	7.04	.008*	–	–	–	–
NLR	–	–	–	–	1.46	1.14–1.86	9.27	.002*
Alb	1.03	0.84–1.25	0.06	.81	0.88	0.78–1.00	4.14	.042*
PCT	3.68	1.02–13.24	3.97	.046*	–	–	–	–
hs-CRP	1.67	1.05–2.64	4.76	.03	–	–	–	–

Patients were defined as treated with maintenance hemodialysis.

Alb = albumin, hs-CRP = hypersensitive c-reactive protein, NLR = neutrophil-lymphocyte ratio, PCT = procalcitonin, RBC = red blood cell, WBC = white blood cell.

* A *P* of <.05 represents significant variance in model 1 or model 2 used multivariate logistic regression analysis.

Table 5

Comparison of heart rate and NLR, PCT, CRP, patients before and after treatment.

Group	**N**	**PCT (ng/mL)**	**CRP (ng/mL)**	**Heart rate**	**NLR**
Prior treatment	49	1.4 (0.7–3.3)	22.1 (7.1–63.3)	90 (80–102)	6.3 (4.2–11.2)
Post-treatment	49	0.5 (0.1–1.0)	2.7 (0.7–6.0)	80 (76–84)	3.2 (2.5–4.7)
Z	–	–4.461	–5.584	–3.991	–5.349
P	–	<.001*	<.001*	<.001*	<.001*

Patients were defined as treated with maintenance hemodialysis.

CRP = hypersensitive c-reactive protein, NLR = neutrophil-lymphocyte ratio, PCT = procalcitonin.

* A *P* of <.05 represents significant variance between the groups.

Table 6

Single factor logistic regression analysis of NLR by Indicators.

Category	**B**	**OR**	**SE**	**95%CI**	**Wald**	***P***
Hb	–0.03	0.97	0.10	0.94–0.99	10.95	.001*
RBC	–0.92	0.40	0.28	0.23–0.69	10.73	.001*
WBC	0.46	1.59	0.12	1.26–2.00	15.57	<.001*
Alb	–0.09	0.91	0.04	0.85–0.98	6.28	.012*
PCT	0.51	1.66	0.20	1.11–2.47	6.12	.013*
hs-CRP	0.02	1.02	0.01	1.01–1.04	6.42	.011*

Patients were defined as treated with maintenance hemodialysis.

Alb = albumin, CI = confidence interval, Hb = haemoglobin, hs-CRP = hypersensitive c-reactive protein, NLR = neutrophil-lymphocyte ratio, PCT = procalcitonin, RBC = red blood cell, WBC = white blood cell.

* A *P* of <.05 represents significant variance used single factor logistic regression analysis.

Table 7

Length of hospital stay in dialysis patients.

	Day in hospital			***P***	**Statistic**
NLR	**Min**	**Max**	**Ave**	**<.001***	**Z = –3.519**
<4.19	2	15	8.74		
≥4.19	4	42	14.28		

Patients were defined as treated with maintenance hemodialysis.

NLR = neutrophil-lymphocyte ratio.

* A *P* of <.05 represents significant variance between the groups.

Table 8

NLR, CRP, PCT, and NLR combined with CRP or PCT the diagnosis of pulmonary infection.

Index	AUC	cut-off value	Sensitivity (%)	Specificity (%)	95%CI	Youden index	*P*
CRP	0.881	3.23	87.76	96.08	0.801–0.937	0.838	<.001*
PCT	0.95	0.18	93.88	88.24	0.888–0.984	0.821	<.001*
NLR	0.829	5.52	65.31	94.12	0.740–0.897	0.5942	<.001*
Combined NLR and CRP	0.920	0.434	87.76	100	0.848–0.965	0.878	<.001*
Combined NLR and PCT	0.944	0.427	87.76	96.08	0.879–0.980	0.838	<.001*

Patients were defined as treated with maintenance hemodialysis.

AUC = area under the curve, CI = confidence interval, CRP = hypersensitive c-reactive protein, NLR = neutrophil-lymphocyte ratio, PCT = procalcitonin, RBC = red blood cell, WBC = white blood cell.

* A *P* of <.05 represents significant variance between the groups used ROC analysis.

immune function of phagocytes, NK, and lymphocytes.[43–46] A study by Scott Sibbel et al[14] reported that Hb levels were generally low in uremic patients complicated with pulmonary infection.

Another study recorded that the prevalence of protein-energy malnutrition was 18 – 75% in dialysis patients,[47–49] which has been shown to increase the risk of death in dialysis patients.[50] Low albumin has been used as an important predictor of death in ESRD patients,[51] which increases the risk of pulmonary infection in dialysis patients.[52] We speculated that this may be linked to the body microinflammatory state, endothelial/oxidative dysfunction, and malnutrition in MHD patients.[53] Moreover, low albumin reflects malnutrition as well as limited cell proliferation capacity and reduced protein synthesis, which may predispose MHD patients to low immune function, leading to pneumonia and death.[47,52] Albumin is the main component of the sulfhydryl group that can scavenge oxygen and nitrogen radicals.[54] Thus, low albumin weakens this clearance function, making patients susceptible to infection.

10.2. Application and significance of blood NLR in pulmonary infection in maintenance hemodialysis patients

The blood NLR, WBC, PCT, and hs-CRP in the infected group was significantly higher than that in the non-infected group, suggesting that NLR can be used as an index to evaluate the inflammatory status of MHD patients.[55] Additionally, blood WBC, PCT, and hs-CRP are risk factors for NLR. The NLR was positively correlated with PCT, hs-CRP, and age, while on the other hand, it was negatively correlated with Hb, RBC, and Alb. A study has noted that downregulation of RBC, Hb, and Alb expression will lead to low immune function in the body, thus leading to an increased probability of pulmonary infection in dialysis patients.[56] Elsewhere, the experimental model implies that inflammatory cells may regulate CRP levels by secreting pro-inflammatory factors such as TNF-α and IL-6.[57,58] Remarkably, Turkmen et al recorded a positive correlation between NLR and TNF-α in HD patients.[25] In this study, the relationship between NLR and CRP was positively correlated, while that of NLR with Alb levels was significantly negatively correlated. This signifies that albumin is a negative acute-phase protein, which supports the concept of the malnutrition-inflammatory complex in HD patients.[57]

Furthermore, we found that NLR, PCT, CRP, and heart rate after treatment in patients with pulmonary infection were significantly lower than before treatment. Therefore, we posit that NLR as traditional classical inflammatory indicators, for instance, CRP and PCT, can be applied as an indicator to assess the efficacy of infection treatment in dialysis patients. In this work, NLR was positively correlated with length of hospital stay. Of note, we identified that when the NLR value is greater than 5.52, the possibility of body infection is great, hence we require a more sensitive infection prediction index for hemodialysis patients through routine blood examination. In comparison with CRP and PCT, the cost of this test has a certain economy and convenience, therefore it has potential application value in guiding clinical anti-infection treatment.

10.3. The diagnostic effect of blood NLR, hs-CRP, and PCT on pulmonary infection in MHD patients

The results of ROC suggest that the use of NLR to assess pulmonary infection in dialysis patients is valuable. Furthermore, the AUC of NLR combined with hs-CRP was higher and the specificity increased than that of NLR and hs-CRP alone. Similarly, the AUC of NLR combined with PCT was higher than that of NLR alone, and its sensitivity and specificity were considerably higher than that of a single diagnosis.

10.4. Limitations

Despite the promising preliminary result, this study has some shortcomings that need to be mentioned. First, we acknowledge that the sample size was relatively small and was a single-center cross-sectional study. Second, the selection of relevant data to be included in the study may be restricted by uncontrollable factors, thus the related research results lack the representativeness of the whole population. Third, the types of pulmonary infection were not further subdivided based on the etiology results. Finally, we did not subdivide the patients with mild and severe lung sensation, while the scoring index related to the specific clinical and various vital signs of the patients with infection, is not well achieved.

11. Conclusions

In summary, the present work demonstrates that blood WBC, NEU, NLR, PCT, and hs-CRP are risk factors leading to pulmonary infection in MHD patients, while Hb, RBC, LYM, and Alb are protective factors. There was a positive correlation between NLR with age, PCT, and hs-CRP. On the other hand, there was a negative correlation between NLR with blood Hb, RBC, and Alb, indicating that NLR is an independent risk factor for pulmonary infection in MHD patients.

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