Original Article

Neutrophil/lymphocyte ratio is helpful for predicting weaning failure: a prospective, observational cohort study

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Background: To assess the usefulness of the neutrophil/lymphocyte ratio (NLR), a marker of inflammation and/or stress, for predicting weaning failure in patients receiving invasive mechanical ventilation (IMV), compared to levels of leukocytes and C-reactive protein (CRP).

Methods: This observational prospective cohort study was conducted from July 2013 to December 2016 in an intensive care unit in China, enrolling 269 consecutive patients receiving IMV. Patients underwent a spontaneous breathing trial (SBT) if they were ready to wean, and underwent extubation if they passed the SBT. The evaluated markers were measured immediately prior to SBT, and compared between weaning-failure and weaning-success patients. Receiver-operating characteristic (ROC) curve and logistic regression analyses were used to evaluate the ability of these markers to predict weaning failure.

Results: In all, 94 (34.9%) patients failed the weaning process (66 failed SBT and 28 presented with post-extubation respiratory distress). NLR was a better predictor of failure (area under the ROC curve, 0.69; 95% CI, 0.62–0.76) than leukocyte levels (0.60, 0.53–0.67) and CRP values (0.58, 0.51–0.65). NLR >11, leukocyte counts >10.5×10^9/L, and CRP >58 mg/L prior to weaning had the best combination of sensitivity (73%, 64%, and 63%, respectively), specificity (59%, 55%, and 63%), positive predictive value (49%, 43%, and 48%), negative predictive value (81%, 74%, and 76%), and diagnostic accuracy (64%, 58%, and 63%) for predicting weaning failure. However, only NLR >11 (odds ratio, 5.91; 95% CI, 3.08–11.33; P<0.001) was an independent predictor of weaning failure in the adjusted logistic regression model.

Conclusions: NLR may be a useful marker for predicting weaning failure, and weaning at NLR >11 might be considered with caution. Further study with a larger sample size and with weaning outcome as a variable of concern is warranted. Trial registration: ClinicalTrials.gov identifier: NCT02981589.

Keywords: Invasive mechanical ventilation (IMV); weaning failure; spontaneous breathing trial (SBT); post-extubation respiratory distress; neutrophil/lymphocyte ratio (NLR); leukocytes; C-reactive protein (CRP)

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Introduction

Weaning from invasive mechanical ventilation (IMV) remains a huge challenge to critical care physicians (1,2). The weaning process can account for 40–50% of the total duration of IMV, which can delay extubation and lead to complications and/or death (2-4). Although spontaneous breathing trials (SBTs) are reliable tests for judging weaning outcomes, 13% of patients with successful SBT results still require reintubation (2,5). Moreover, roughly 30% of IMV patients experience difficult or prolonged weaning, which can lead to morbidities or even death (2). Hence, it is of significant importance to enhance the accuracy of methods predicting weaning outcome.

The ratio of neutrophils to lymphocytes (NLR) in peripheral blood samples may correlate closely with systematic inflammation and/or stress and has been shown to have promising predictive ability under several clinical circumstances as a simple, inexpensive, and clinically accessible marker (6-21). In critically ill patients, NLR has a robust association with the severity of disease andmortality (7,9). In an emergency care setting, NLR has been found to be more accurate for predicting bacteremia and the severity of disease than other markers (10,11). Among sepsis patients, the ratio is independently correlated with dreadful clinical prognoses (12). Among patients with chronic obstructive pulmonary disease (COPD), it may predict the severity of disease and the potential for exacerbations (13,14). In addition, NLR has been shown to be a valuable prognostic marker for various chronic conditions ranging from oncological to cardiovascular diseases (6,15-21).

Patients would show an inflammatory response when suffering from systematic or local infections and when undergoing endotracheal intubation and subsequent IMV (7,22-24). Moreover, such a response would become more severe in the presence of IMV-related complications such as ventilator-induced lung injury (25). In addition, previous studies (26-28) have shown that patients who fail weaning (WF) experience higher pulmonary and cardiovascular stress than those who are successfully weaned (WS). Hence, patients with signs of such responses might be prime candidates for WF. However, to date, the relationship between inflammation and/or stress and weaning outcome does not appear to have been investigated.

We hypothesized that NLR would be higher in WF patients than in WS patients. Accordingly, we evaluated the utility of NLR for predicting WF in patients receiving IMV, compared to traditional inflammatory markers such as leukocyte counts and levels of C-reactive protein (CRP).

Methods

Study design

We performed an observational prospective cohort study from July 2013 to December 2016 in the 12-bed intensive care unit (ICU) of Beijing Chao-Yang Hospital in China. A total of 269 consecutive patients receiving IMV were enrolled, with closest relatives or other surrogates providing written informed consent. Our hospital's ethics committee approved our protocol (No. 2013-KE-24), and the study was retrospectively registered at ClinicalTrials.gov (NCT02981589).

Patients

Inclusion and exclusion criteria are shown in *Table 1*.

Weaning protocol

All enrolled patients completed a 2 h SBT during which they could breathe spontaneously through a T-tube circuit with the FiO_2 adjusted to match each patient's corresponding IMV setting. During the trial, respiratory rate (RR), systolic blood pressure (SBP), heart rate (HR), pulse oxymetry, five-lead electrocardiographic tracing, and clinical signs were closely monitored. Arterial blood gas measurements were made before and at the very end of SBT. Trials were considered to have failed and were terminated when a patient's condition worsened and met the SBT failure criteria (see *Table 1* for definition) at any time during the 2 h. Otherwise, patients were considered to have passed the SBT and were extubated.

Patients were monitored closely for at least 48 h after extubation. If patients experienced respiratory distress (see *Table 1* for definition), rescue noninvasive ventilation (NIV) was considered; if their condition worsened and they met the reintubation criteria (see *Table 1* for definition), they were reintubated.

The decision to start SBT, reinstitute IMV during or at the end of SBT, extubate/reintubate patients, or attempt rescue NIV was left to the attending physician, who was blinded to the study.

Data collection and definitions

At enrollment, patients' baseline characteristics were recorded, including demographic data, acute physiology and chronic health evaluation II (APACHE II) score, IMV

Table 1 Inclusion and exclusion criteria, and select clinical definitions

Criteria type/condition	Criteria/definition
Inclusion criteria	Presence of all of the parameters that follow:
	IMV for more than 48 h
	Resolution of causes of acute respiratory failure
	Adequate cough reflex
	Absence of excessive tracheobronchial secretion (e.g., airway suctioning less frequently than every 2 h)
	Adequate oxygenation (e.g., arterial oxygen saturation >90% or PaO_2/FiO_2 ≥150 mmHg, at FiO_2 ≤0.4 and PEEP ≤8 cmH_2O)
	Adequate ventilatory status (e.g., RR ≤35 breaths/min with tidal volume ≥ 5 mL/kg predicted body weight and no significant respiratory acidosis)
	Stable hemodynamics (e.g., HR <120 beats/min; SBP, 90–160 mmHg; no or minimal vasopressor use)
	Adequate mentation (e.g., arousable or Glasgow coma scale ≥13 with no continuous sedative infusions)
	Body temperature <38 ℃
	Hemoglobinemia ≥8–10 g/dL
	Acceptable electrolyte levels
Exclusion criteria	Presence of ≥1 parameter that follows:
	Age <18 years old
	Pregnant
	Tracheotomy or other upper airway disorders
	Active upper gastrointestinal bleeding
	Lack of cooperation
	Decision to limit active treatment
	Refusal to authorize research
SBT failure	Presence/persistence of ≥1 parameter that follows:
	Arterial pH <7.32 with $PaCO_2$ ≥10 mmHg above baseline
	SpO_2 <90% or PaO_2 ≤60 mmHg at a FiO_2 ≥0.4
	HR >140 beats/min or ≥20% above/below baseline
	RR >35 breaths/min or ≥50% over baseline
	SBP <90 mmHg or >180 or ≥20% above/below baseline
	Paradoxical abdominal/thoracic movement or use of accessory respiratory muscles
	Diaphoresis, agitation, or reduced alertness
Post-extubation respiratory distress	Presence/persistence of ≥2 parameters that follow:
	Arterial pH <7.35 with $PaCO_2$ >45 mmHg or >20% above baseline
	RR >30 breaths/min or ≥50% above baseline
	PaO_2 <60 mmHg or SpO_2 <90% at FiO_2 ≥0.5
	Intercostal retractions, accessory respiratory muscle use, or paradoxical abdominal/ thoracic movement
	Diaphoresis, agitation, or reduced alertness

Table 1 *(continued)*

Table 1 *(continued)*

Criteria type/condition	Criteria/definition
Reintubation	Presence/persistence of ≥1 parameter that follows:
	Respiratory or cardiac arrest
	Severe hemodynamic instability despite adequate fluid repletion and use of vasoactive agents
	RR >40 breaths/min persistently or <8 breaths/min
	Arterial pH ≤7.20 with a progressive increase in $PaCO_2$
	PaO_2 <50 mmHg despite maximum tolerated supplemental oxygen
	Clinical signs of severely reduced alertness (e.g., stupor, delirium, coma)

FiO_2, fraction of inspired oxygen; HR, heart rate; IMV, invasive mechanical ventilation; $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension; PEEP, positive end-expiratory pressure; RR, respiratory rate; SBP, systolic blood pressure; SpO_2, peripheral oxygen saturation.

duration prior to weaning, underlying diseases, and causes of IMV. Prior to weaning, we recorded vital signs and arterial blood gas data. After extubation, the following was recorded: success or failure of weaning, length of stay (in ICU and hospital), mortality (in ICU and hospital), and 28-day survival.

Peripheral venous blood samples were drawn at the beginning of SBT to measure complete blood cell counts and CRP levels. NLR was determined by dividing the total number of neutrophils by the total number of lymphocytes.

The primary outcome was WF defined as the need for rescue NIV, reintubation <48 h post-extubation, or reinstitution of IMV during or at the very end of SBT (2). Secondary outcomes included length of stay (in ICU and hospital), mortality (in ICU and hospital), and 28-day survival.

Statistical analyses

To compare continuous variables, the Kolmogorov–Smirnov test was used to test the normality of the data, Levene's test was applied to assess homogeneity of variance, Student's *t*-test was used for normally distributed data (expressed as means ± standard deviations), and the Mann-Whitney U test was utilized for non-normally distributed data [expressed as medians (with 25^{th}–75^{th} percentiles)]. The Chi-square test (with/without continuity correction, as needed) was employed to compare qualitative or categorical variables (expressed as absolute values with percentages).

Correlations between NLR and leukocytes/CRP were investigated using Spearman's correlations, and the results are displayed as correlation coefficients and P values. The utility of each marker (NLR, leukocyte levels, and CRP) for predicting WF was analyzed based on receiver-operating characteristic (ROC) curves. For each ROC curve, we calculated the optimal cutoff values, Youden's index, sensitivity, specificity, diagnostic accuracy, the area under the curve (AUC, with 95% CIs), positive/negative predictive value, and the likelihood ratio of positive/negative tests.

Next, to investigate the potential associations between each of these markers and WF, we first conducted univariate analyses, which resulted in an odds ratio (95% CI) for each variable. Then, to determine if any of these markers were independently associated with WF, we conducted multivariate analyses applying a conditional forward stepwise model (with an entry level of 0.05 and a removal level of 0.10), which resulted in adjusted odds ratios (95% CIs). These analyses were performed with all possible confounders (e.g., age, gender, chronic respiratory disorders, postoperative respiratory failure, neurological disease, APACHE II score at baseline, and RR, SpO_2, HR, SBP, pH, $PaCO_2$, and PaO_2/FiO_2 prior to weaning) as covariates. Kaplan-Meier 28-day survival curves were constructed according to weaning outcome, NLR, leukocyte counts, and CRP levels; log-rank tests were used to compare the curves.

All analyses were two-tailed, and differences were considered to be statistically significant at P<0.05. The SPSS software package (version 19.0, SPSS, Chicago, IL, USA) was used for all statistical analyses.

Results

Patient characteristics and weaning outcome

A total of 269 patients were included in the study (see *Figure 1*

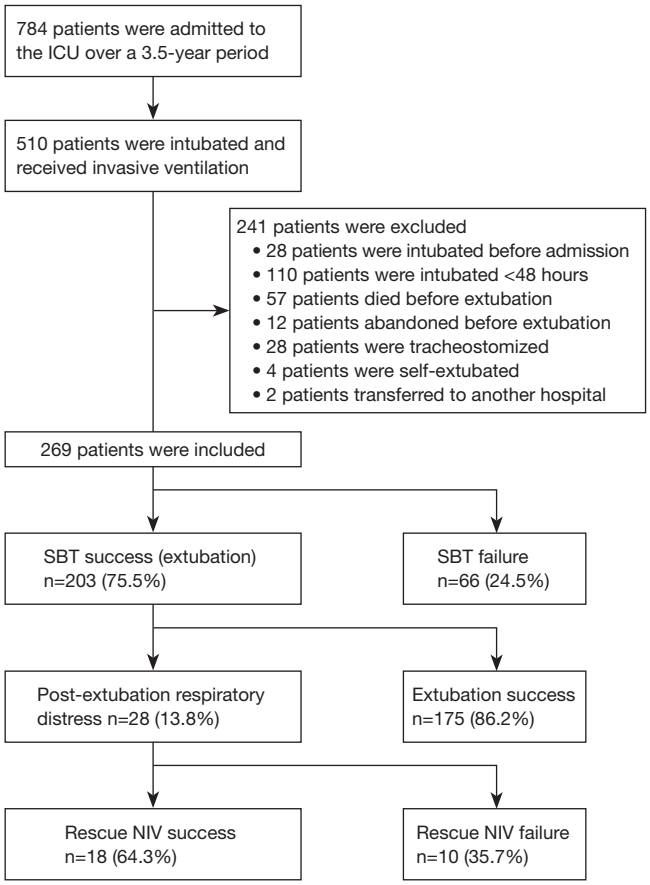

Figure 1 Weaning outcome flow chart. ICU, intensive care unit; NIV, noninvasive ventilation; SBT, spontaneous breathing trial.

for a flow chart of patient selection). Of these, 94 (34.9%) failed the weaning process (66 failed the SBT and 28 presented with post-extubation respiratory distress). Reasons for post-extubation respiratory distress included hypoxemia (n=12), respiratory acidosis (n=10), excess respiratory secretions (n=3), aspiration (n=2), and pulmonary edema (n=1). In 18 of these patients, reintubation was prevented via rescue NIV; the rest were ultimately reintubated.

Table 2 summarizes the baseline characteristics of the study population. Compared to WS patients, the WF group had higher rates of chronic respiratory failure and neurological disease; lower rates of postoperative respiratory failure; higher scores on APACHE II; and longer IMV durations prior to weaning. RR, SpO_2, HR, SBP, pH, $PaCO_2$, and PaO_2/FiO_2 prior to weaning significantly differed between the two groups (*Table 3*).

Pre-weaning leukocyte and CRP levels, and NLR

As shown in *Figure 2* and *Table 3*, WF patients had higher NLRs (P<0.001), leukocyte counts (P=0.006), and CRP levels (P=0.027) than WS patients. More specifically, they had higher neutrophil counts (P=0.001), a higher percentage of neutrophils among total leukocyte levels (P<0.001), lower overall lymphocyte counts (P=0.001), and a lower percentage of lymphocytes among total leukocyte levels (P<0.001) (*Table 3*). There were significant positive

Table 2 Baseline characteristics

Characteristic	Weaning failure (n=94)	Weaning success (n=175)	P
Male, n (%)*	59 (62.8)	93 (53.1)	0.129
Age, years [median, 25th–75th percentiles]**	77 [66–81]	73 [63–80]	0.118
APACHE II score on admission (mean ± SD)***	21±8	19±7	0.008
IMV duration prior to weaning, days [median, 25th–75th percentiles]**	5 [3–11]	2 [2–6]	<0.001
Underlying disease, n (%)*			
Chronic respiratory disorders	41 (43.6)	55 (31.4)	0.047
COPD	32 (34.0)	45 (25.7)	0.150
Non-COPD	9 (9.6)	10 (5.7)	0.239
Chronic heart disorders	28 (29.8)	51 (29.1)	0.697
Chronic kidney disease	22 (23.4)	34 (19.4)	0.444
Immunosuppression‡	8 (8.5)	16 (9.1)	0.862
Diabetes mellitus	28 (29.8)	38 (21.7)	0.142

Table 2 *(continued)*

Table 2 *(continued)*

Characteristic	Weaning failure (n=94)	Weaning success (n=175)	P
Cause of mechanical ventilation, n (%)*			
Exacerbation of chronic respiratory disorders	31 (33.0)	42 (24.0)	0.114
Pneumonia	22 (23.4)	35 (20.0)	0.515
Sepsis	13 (13.8)	31 (17.7)	0.412
Congestive heart failure	10 (10.6)	15 (8.6)	0.578
Postoperative respiratory failure	10 (10.6)	43 (24.6)	0.006
Neurological disease	5 (5.3)	2 (1.1)	0.040
Cardiac arrest	2 (2.1)	4 (2.3)	1.000
Other†	1 (1.1)	3 (1.7)	1.000

*, Chi-square test; **, Mann-Whitney U test; ***, Student's *t*-test. ‡, immunosuppression included hematological malignancy (n=5), solid-organ transplantation (n=2) and chemotherapy for a solid tumor (n=1) in the weaning-failure (WF) group, and hematological malignancy (n=9), solid-organ transplantation (n=3), chemotherapy for a solid tumor (n=2), and immunosuppressive treatments for connective tissue disease (n=2) in the weaning-success (WS) group; †, other causes of mechanical ventilation included thoracic trauma (n=1) in the WF group, and gastrointestinal bleeding (n=2) and drug overdose (n=1) in the WS group. APACHE, acute physiology and chronic health evaluation; COPD, chronic obstructive pulmonary disease; IMV, invasive mechanical ventilation; SD, standard deviation.

Table 3 Patient data before weaning

Variable	Weaning failure (n=94)	Weaning success (n=175)	P
Vital signs*			
RR, breaths/min	21 [20–24]	20 [17–23]	0.034
SpO_2, %	98 [98–99]	99 [98–100]	<0.001
HR, beats/min	93 [86–96]	86 [78–97]	0.009
SBP, mmHg	127 [115–140]	133 [122–146]	0.001
Arterial blood gas			
pH*	7.44 [7.43–7.46]	7.45 [7.42–7.48]	0.020
$PaCO_2$, mmHg (mean ± SD)**	44±9	39±8	<0.001
PaO_2/FiO_2, mmHg*	243 [204–289]	302 [246–363]	<0.001
Laboratory findings*			
Leukocyte count, $\times 10^9$/L	11.7 [8.6–14.4]	10.0 [7.7–12.6]	0.006
Neutrophil count, $\times 10^9$/L	10.3 [7.8–13.2]	8.6 [6.3–11.0]	0.001
Lymphocyte count, $\times 10^9$/L	0.7 [0.4–0.9]	0.8 [0.6–1.2]	0.001
Neutrophils, % of leukocyte count	89 [85–93]	86 [80–90]	<0.001
Lymphocytes, % of leukocyte count	6 [3–8]	9 [5–12]	<0.001
NLR	15 [10–31]	10 [6–18]	<0.001
CRP, mg/L	61 [32–80]	42 [17–87]	0.027

Data are medians [25^{th}–75^{th} percentiles] unless otherwise noted. *, Mann-Whitney U test, **; Student's *t*-test. CRP, C-reactive protein; FiO_2, fraction of inspired oxygen; NLR, neutrophil/lymphocyte ratio; $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension; HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; SD, standard deviation; SpO_2, peripheral oxygen saturation.

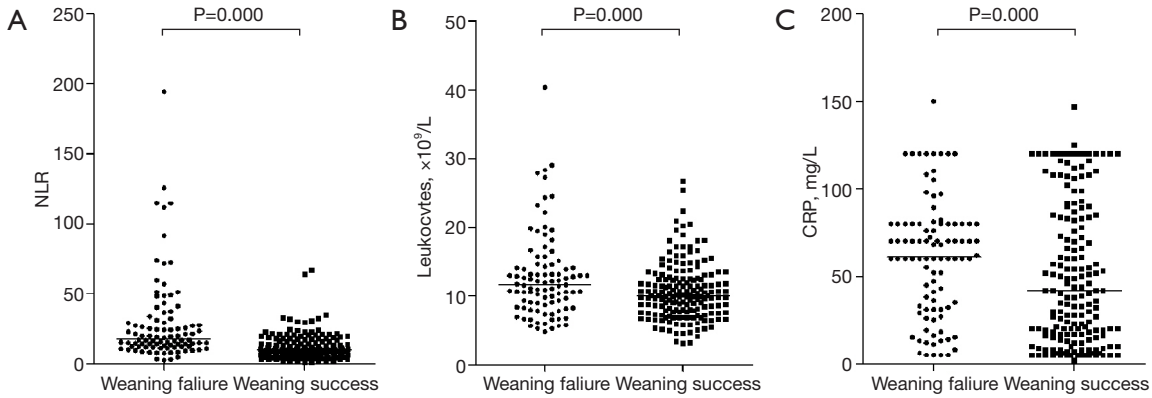

Figure 2 NLR (A), leukocyte counts (B), and CRP levels (C) before spontaneous breathing trial in patients with weaning success or failure. Horizontal bars represent median values. CRP, C-reactive protein; NLR, neutrophil/lymphocyte ratio.

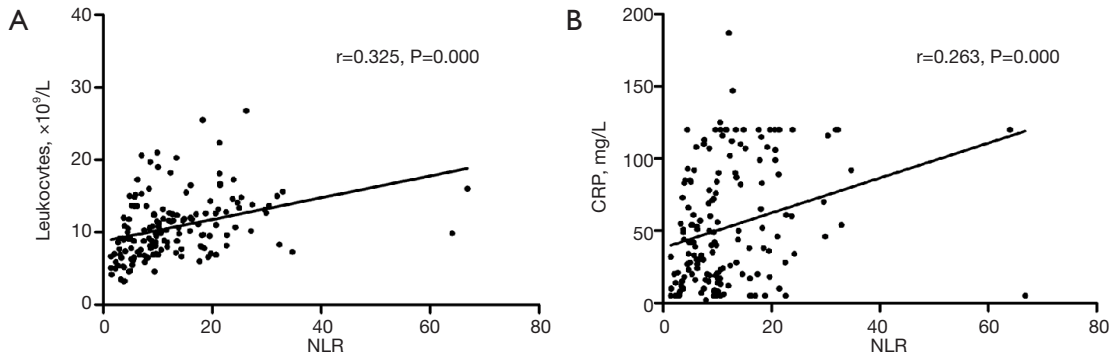

Figure 3 Correlations between NLR and leukocyte counts (A) and CRP (B) before spontaneous breathing trial in weaning-success patients. CRP, C-reactive protein; NLR, neutrophil/lymphocyte ratio.

correlations between NLR and leukocyte count (rho =0.325, P<0.001) and CRP (rho =0.263, P<0.001) in WS patients (*Figure 3*), and between NLR and CRP (rho =0.208, P=0.044) in WF patients (*Figure 4*). NLR and leukocyte count (rho =0.198, P=0.056) also tended to be correlated in WF patients, but the relation did not reach statistical significance (*Figure 4*).

Predictive ability of NLR, leukocyte counts, and CRP levels for WF

The ROC curves for NLR, leukocytes, and CRP are presented in *Figure 5*. The AUC of the NLR ROC curve (0.69; 95% CI, 0.62–0.76) was higher than that of leukocytes (0.60; 95% CI, 0.53–0.67) and CRP (0.58; 95% CI, 0.51–0.65). The best combination of cut-off values that resulted in optimal diagnostic accuracy (63%, 58%, and 64%, respectively), positive predictive value (48%, 43%, and 49%), negative predictive value (76%, 74%, and 81%), specificity (63%, 55%, and 59%), and sensitivity (63%, 64%, and 73%) for predicting WF was CRP >58 mg/L, leukocyte counts >10.5×10^9/L, and NLR >11 prior to weaning (*Table 4*).

According to univariate analyses, patients with NLR >11, leukocyte counts >10.5×10^9/L, and CRP >58 mg/L had a higher probability of WF (*Table 5*). According to multivariate analyses, only NLR >11 was an independent predictor of WF (*Table 5*).

Table 6 shows the baseline and weaning characteristics of the patients according to NLR cutoff values. Compared to patients with NLR ≤11, patients with NLR >11 were older and had a longer IMV duration prior to weaning and higher HR but lower pH and rate of postoperative respiratory failure. The WF rate was significantly higher in patients with NLR >11 than in those with NLR ≤11 [69/140 (49%) *vs.* 25/129 (19%); P<0.001].

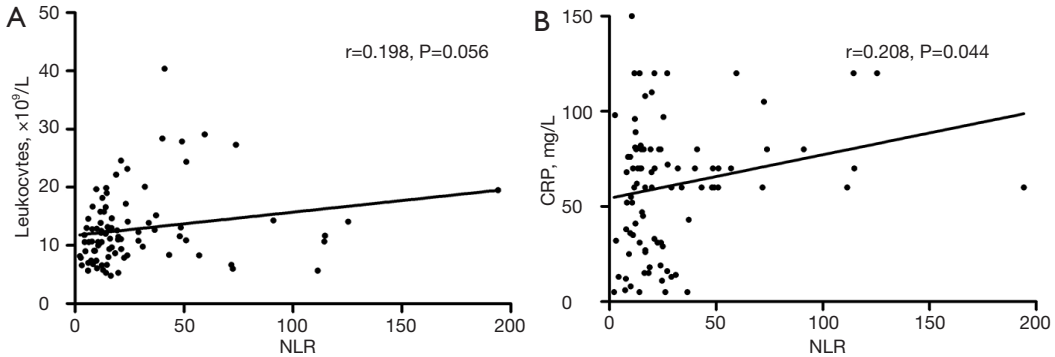

Figure 4 Correlations between NLR and leukocyte counts (A) and CRP (B) before spontaneous breathing trial in weaning-failure patients. CRP, C-reactive protein; NLR, neutrophil/lymphocyte ratio.

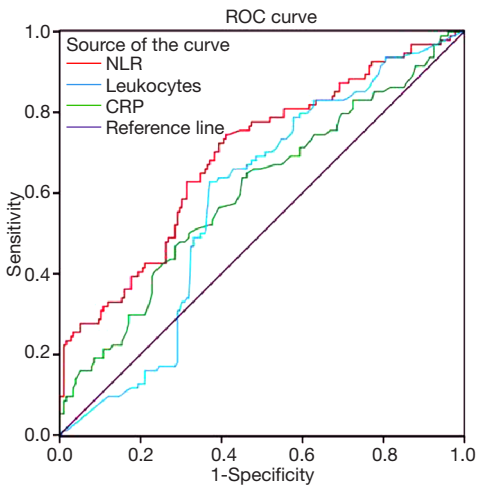

Figure 5 Receiver-operating characteristic curves for NLR, leukocyte counts, and CRP levels for predicting weaning failure. CRP, C-reactive protein; NLR, neutrophil/lymphocyte ratio; ROC, receiver-operating characteristic curve.

Table 4 ROC curve data

Characteristic	NLR	Leukocytes (×10⁹/L)	CRP (mg/L)
Cutoff value	>11	>10.5	>58
Sensitivity, %	73	64	63
Specificity, %	59	55	63
Positive predictive value, %	49	43	48
Negative predictive value, %	81	74	76
Diagnostic accuracy, %	64	58	63
Likelihood ratio of positive test	1.78	1.42	1.70
Likelihood ratio of negative test	0.46	0.65	0.59
Youden's index	0.33	0.19	0.26
AUC	0.69	0.60	0.58
95% CI	0.62–0.76	0.53–0.67	0.51–0.65

AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; NLR, neutrophil/lymphocyte ratio; ROC, receiver-operating characteristic.

Patient outcome

Compared to WS patients, the WF group had higher ICU mortality [33/94 (35%) *vs.* 18/175 (10%); P<0.001] and hospital mortality [40/94 (43%) *vs.* 24/175 (14%); P<0.001], and longer length of ICU stay {14 [7–26] *vs.* 5 [3–16] days; P<0.001}. The two groups did not differ significantly in hospital stay duration {19 [10–40] *vs.* 16 [11–30] days; P=0.519}. As shown in *Figure 6*, the cumulative survival probability within 28 days after randomization was lower in patients with WF (P<0.001 by log-rank test), NLR >11 (P=0.0067 by log-rank test), leukocyte counts >10.5 ×10^9/L (P=0.002 by log-rank test), and CRP >58 mg/L (P=0.0003 by log-rank test).

Discussion

We believe that this study is the first to exclusively explore the potential of NLR for predicting WF, and one of a few studies to investigate the usefulness of NLR in an ICU. Systemic inflammation and/or stress is commonly present

Table 5 Risk factors for weaning failure

Variable	No. of failures/total (%)	Univariate analysis			Multivariate analysis†		
		Unadjusted OR	95% CI	P	Adjusted OR	95% CI	P
NLR							
≤11	25/129 (19.4)	1.00	–				
>11	69/140 (49.3)	4.04	2.33–6.99	<0.001	5.91	3.08–11.33	<0.001
Leukocytes, $\times10^9$/L							
≤10.5	34/130 (26.2)		–				
>10.5	60/139 (43.2)	2.14	1.28–3.59	0.004	–	–	–
CRP, mg/L							
≤58	35/145 (24.1)	1.00	–				
>58	59/124 (47.6)	2.85	1.70–4.79	<0.001	–	–	–

†, Performed with age, gender, chronic respiratory disorders, postoperative respiratory failure, neurological disease, APACHE II score at baseline, and pre-weaning RR, SpO_2, HR, SBP, pH, $PaCO_2$, and PaO_2/FiO_2 as covariates. Logistic regression was performed on 269 patients: area under the receiver-operating characteristic curve =0.78, sensitivity =63%, specificity =86%, positive predictive value =71%, negative predictive value =82%, correctly classified =78%. APACHE, acute physiology and chronic health evaluation; CI, confidence interval; CRP, C-reactive protein; FiO_2, fraction of inspired oxygen; HR, heart rate; NLR, neutrophil/lymphocyte ratio; OR, odds ratio; $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension; RR, respiratory rate; SBP, systolic blood pressure; SpO_2, peripheral oxygen saturation.

Table 6 Patient data before weaning according to NLR cutoff value

Characteristic	NLR >11 (n=140)	NLR ≤11 (n=129)	P
Male, n (%)*	77 (55.0)	75 (58.1)	0.604
Age, years**	76 [65–82]	73 [62–79]	0.036
APACHE II score on admission (mean ± SD)***	20±7	19±8	0.183
IMV duration prior to weaning, days**	4 [2–10]	2 [2–6]	<0.001
Underlying disease, n (%)*			
Chronic respiratory disorders	52 (37.1)	44 (34.1)	0.604
COPD	40 (28.6)	37 (28.7)	0.984
Non-COPD	12 (8.6)	7 (5.4)	0.315
Chronic heart disorders	43 (30.7)	36 (28.0)	0.614
Chronic kidney disease	30 (21.4)	26 (20.2)	0.881
Immunosuppression‡	15 (10.7)	9 (7.0)	0.392
Diabetes mellitus	41 (29.3)	25 (19.4)	0.059
Cause of mechanical ventilation, n (%)*			
Exacerbation of chronic respiratory disorders	41 (29.3)	32 (24.8)	0.409
Pneumonia	35 (25.0)	22 (17.1)	0.111
Sepsis	28 (20.0)	16 (12.4)	0.092
Congestive heart failure	11 (7.9)	14 (10.9)	0.398

Table 6 *(continued)*

Table 6 *(continued)*

Characteristic	NLR >11 (n=140)	NLR ≤11 (n=129)	P
Postoperative respiratory failure	15 (10.7)	38 (29.5)	<0.001
Neurological disease	5 (3.6)	2 (1.6)	0.511
Cardiac arrest	3 (2.1)	3 (2.3)	1.000
Other†	2 (1.4)	2 (1.6)	1.000
Vital signs prior to weaning**			
RR, breaths/min	21 [17–22]	21 [17–24]	0.478
SpO_2, %	98 [98–100]	99 [98–100]	0.184
HR, beats/min	93 [84–99]	86 [79–96]	0.003
SBP, mmHg	131 [120–141]	132 [120–142]	0.898
Arterial blood gas prior to weaning			
pH**	7.44 [7.43–7.46]	7.45 [7.42–7.48]	0.009
$PaCO_2$, mmHg (mean ± SD)***	42±8	40±8	0.076
PaO_2/FiO_2, mmHg**	262 [228–333]	292 [229–363]	0.387

Data are medians [25^{th}–75^{th} percentiles] unless otherwise noted. *, Chi-square test; **, Mann-Whitney U test; ***, Student's *t*-test. ‡, Immunosuppression included hematological malignancy (n=9), solid-organ transplantation (n=3), chemotherapy for a solid tumor (n=2), and immunosuppressive treatments for connective tissue disease (n=1) in patients with an NLR >11, and hematological malignancy (n=5), solid-organ transplantation (n=2), chemotherapy for a solid tumor (n=1), and immunosuppressive treatments for connective tissue disease (n=1) in patients with an NLR ≤11; †, other causes of mechanical ventilation included thoracic trauma (n=1) and gastrointestinal bleeding (n=1) in patients with an NLR >11, and gastrointestinal bleeding (n=1) and drug overdose (n=1) in patients with an NLR ≤11. APACHE, acute physiology and chronic health evaluation; COPD, chronic obstructive pulmonary disease; FiO_2, fraction of inspired oxygen; HR, heart rate; IMV, invasive mechanical ventilation; NLR, neutrophil/lymphocyte ratio; $PaCO_2$, arterial carbon dioxide tension; PaO_2, arterial oxygen tension; RR, respiratory rate; SBP, systolic blood pressure; SD, standard deviation, SpO_2, peripheral oxygen saturation.

during IMV, suggesting that it is worthwhile to elucidate the potential association between such responses and weaning outcome (23,28,29). Our main finding that the discriminatory ability of NLR (a marker of inflammation and/or stress) for WF is superior to that of traditional inflammatory markers makes it clear that NLR may be a useful marker for predicting WF, and thus weaning at higher NLRs might be considered with caution.

WF is typically regarded as when a patient fails SBT or must be reintubated within 48 h after extubation (2,30,31). However, prophylactic and curative NIV are frequently attempted during weaning in an ICU, which would partially avert extubation failure and challenge the traditional definition (32-35). Hence, as recommended by an international consensus conference, we defined WF as SBT failure or the resumption of noninvasive or invasive ventilation within 48 h following extubation (2). Such a pragmatic definition is similar to that of previous studies where NIV was not used, but would be more suitable to current clinical practices in ICUs (30,31).

We found that NLR was higher in WF patients than in WS patients, the AUC of the NLR ROC curve was the highest among the evaluated markers, and NLR >11 was the only independent predictor of WF. There may be an underlying causal effect that can explain these findings. Theoretically, inflammation and/or stress tend to trigger increases in neutrophil levels and decreases in lymphocyte levels, resulting in an increase in NLR (11). Furthermore, neutrophilia is caused by demargination and delayed apoptosis of neutrophils, and stimulation of stem cells by growth factors, whereas in lymphopenia, lymphocytes tend to be marginated and redistributed within the lymphatic system and apoptosis is markedly accelerated (36-39). A more severe inflammatory and/or stress response would result in a higher NLR. Such conditions may be caused by certain unresolved inflammatory diseases that cause respiratory failure and prompt IMV, IMV-related complications, and/or the condition of cardiopulmonary

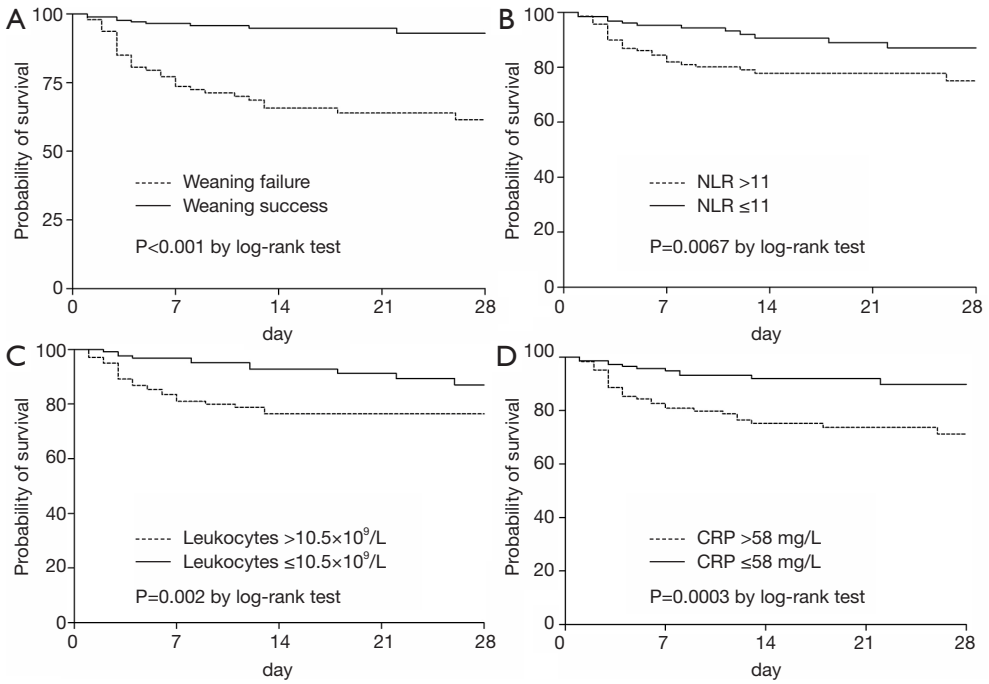

Figure 6 Kaplan-Meier curves for 28-day survival categorized by weaning outcome (A), NLR (B), leukocyte counts (C), and CRP levels (D) before spontaneous breathing trial. CRP, C-reactive protein; NLR, neutrophil/lymphocyte ratio.

stress on which spontaneous breathing capability becomes limited to counterbalance respiratory load (2,25,28). All of these factors could possibly lead to weaning difficulty (2). Accordingly, there would be an independent association between inflammation and/or stress and WF, and thus NLR might have the potential to help predict WF.

Leukocyte levels, a well-known inflammatory marker, are frequently used in current clinical practice (11). We explored this marker's ability to predict WF and compared it to NLR. We found that NLR was a more valuable predictor of WF than leukocyte levels. A possible explanation is that leukocytes mainly represent changes in neutrophils, while NLR represents changes in both neutrophils and lymphocytes (11). Hence, NLR may better indicate inflammatory and/or stress responses. In line with this finding, previous studies have reported that NLR is a better predictor of bacteremia and mortality than leukocyte levels during emergency care (10,11). It also appears to be better than leukocyte counts for predicting the prognosis of cardiovascular disease (40).

CRP is also a conventional systemic marker of inflammation, and its plasma concentration increases in response to inflammation (41). Nevertheless, we found that NLR outperformed CRP in predicting WF, in line with previous studies that have reported that CRP has relatively poor predictive ability for bacteremia and mortality in emergency patients compared to NLR (10,11), and is not superior to using a combination of neutrophilia and lymphocytopenia for predicting bacteremia (42).

Limitations

This study had several limitations. First, considering the single-center nature of the study, our findings should be generalized with caution to other settings. Second, although our hospital has established criteria for all clinical procedures and decisions, each attending physician made personal decisions regarding when to start SBT, extubate/reintubate patients, reinstitute IMV during SBT, or attempt rescue NIV; consequently, it is impossible to guarantee that every patient was managed identically throughout the study. Third, neutrophil levels, also a traditional inflammatory maker, were not compared to NLR because the ratio already includes neutrophils; in addition, changes in leukocyte levels mainly represent changes in neutrophils (11). Finally, certain co-morbidities (e.g., malnutrition, hematological disease) would affect the inflammatory responses of circulating white blood cells and even change

the NLR, but relevant data were absent; nonetheless, this could confound our findings (43,44). However, it is difficult to obtain all data on patients in an ICU.

Conclusions

This study offers the first experimental data indicating that the discriminatory ability of NLR in WF is superior to that of leukocyte counts and CRP levels, and NLR >11 was an independent predictor of WF. We suggest that NLR may be a useful predictor of WF and that weaning at NLR >11 might be considered with caution. However, further study with a larger sample size is warranted to determine whether NLR as a biomarker for predicting WF would improve weaning outcomes.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: This study was approved by the ethics committee of Beijing Chao-Yang Hospital (No. 2013-KE-24), and closest relatives or other surrogates provided written informed consent, if appropriate.

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