

**EFFECT OF PULMONARY-SPECIFIC ENTERAL NUTRITION ON NEUTROPHIL-TO-LYMPHOCYTE RATIO AND BLOOD LACTATE LEVELS IN MECHANICALLY VENTILATED PNEUMONIA PATIENTS**Achmad Mudassir Muchlis<sup>1\*</sup>, Ceva Wicaksono Pitoyo<sup>1</sup>, Dita Aditiansih<sup>2</sup>, Hamzah Shatri<sup>3</sup>, Mira Yulianti<sup>1</sup>, Hasan Maulahela<sup>4</sup>, Anna Ariane<sup>5</sup>, Edy Rizal Wahyudi<sup>6</sup><sup>1</sup> Division of Respiriology and Critical Care, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo National Hospital, Jakarta, Indonesia.<sup>2</sup> Department of Anesthesiology and Intensive Care, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo National Hospital, Jakarta, Indonesia.<sup>3</sup> Division of Psychosomatic Medicine and Palliative Care, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo National Hospital, Jakarta, Indonesia.<sup>4</sup> Division of Gastroenterology and Hepatology, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo National Hospital, Jakarta, Indonesia.<sup>5</sup> Division of Rheumatology, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo National Hospital, Jakarta, Indonesia.<sup>6</sup> Division of Geriatric, Department of Internal Medicine, Faculty of Medicine, Universitas Indonesia - Cipto Mangunkusumo National Hospital, Jakarta, Indonesia.**ABSTRACT**

**Background:** Pneumonia remains a major cause of morbidity and mortality, particularly among critically ill patients requiring mechanical ventilation. Systemic inflammation and metabolic dysfunction may be reflected by biomarkers such as neutrophil-to-lymphocyte ratio (NLR) and blood lactate levels. Pulmonary-specific enteral nutrition has been proposed to improve metabolic responses in these patients. This study aimed to evaluate its effect on NLR and blood lactate levels in mechanically ventilated pneumonia patients.

**Methods:** A double-blind randomized controlled trial was conducted in the intensive care and high care units of a tertiary referral hospital in Jakarta, Indonesia. Adult mechanically ventilated pneumonia patients were randomized to receive either pulmonary-specific enteral nutrition or standard enteral nutrition. NLR and blood lactate levels were measured on days 1, 3, and 5. Within-group comparisons were analyzed using the Friedman

test, while between-group comparisons were assessed using the Mann–Whitney U test.

**Results:** Of 56 randomized patients, 46 completed the study and were included in the final analysis (24 intervention vs. 22 control). No significant differences in NLR changes were observed between groups during the observation period. However, blood lactate dynamics differed significantly between groups at the day 3–5 interval ( $p = 0.017$ ) and cumulatively from day 1 to day 5 ( $p = 0.037$ ), with the intervention group demonstrating a more stable decline in lactate levels.

**Conclusion:** Pulmonary-specific enteral nutrition was associated with improved lactate dynamics, suggesting better metabolic stability in mechanically ventilated pneumonia patients, although no significant effect on NLR was observed.

**Keywords:** Pneumonia; Enteral Nutrition; Mechanical Ventilation; Neutrophil-to-Lymphocyte Ratio; Lactate

**ABSTRAK**

**Latar Belakang:** Pneumonia masih menjadi penyebab utama morbiditas dan mortalitas, terutama pada pasien kritis yang memerlukan ventilasi mekanik. Inflamasi sistemik dan disfungsi metabolik dapat tercermin melalui biomarker seperti neutrophil-to-lymphocyte ratio (NLR) dan kadar laktat darah. Nutrisi enteral spesifik paru telah diusulkan untuk memperbaiki respons metabolik pada pasien tersebut. Penelitian ini bertujuan untuk mengevaluasi pengaruh nutrisi enteral spesifik paru terhadap NLR dan kadar laktat darah pada pasien pneumonia dengan ventilasi mekanik.

**Metode:** Uji klinis acak tersamar ganda dilakukan di unit perawatan intensif dan high care unit rumah sakit rujukan tersier di Jakarta, Indonesia. Pasien dewasa dengan pneumonia yang menggunakan ventilasi mekanik diacak untuk menerima nutrisi enteral spesifik paru atau nutrisi enteral standar rumah sakit. Pemeriksaan NLR dan kadar laktat darah dilakukan pada hari ke-1, ke-3, dan ke-5. Analisis perubahan dalam kelompok dilakukan menggunakan uji Friedman, sedangkan perbandingan antar kelompok menggunakan uji Mann–Whitney.

**Hasil:** Dari 56 pasien yang menjalani randomisasi, 46 pasien menyelesaikan protokol penelitian dan dianalisis lebih lanjut, terdiri atas 24 pasien pada kelompok intervensi dan 22 pasien pada kelompok kontrol. Tidak ditemukan perbedaan bermakna pada perubahan NLR antar kelompok selama periode observasi. Namun, dinamika kadar laktat darah berbeda bermakna antar

kelompok pada interval hari ke-3 hingga ke-5 ( $p = 0,017$ ) dan secara kumulatif dari hari ke-1 hingga ke-5 ( $p = 0,037$ ), dengan kelompok intervensi menunjukkan penurunan kadar laktat yang lebih stabil.

**Kesimpulan:** Nutrisi enteral spesifik paru berhubungan dengan perbaikan dinamika laktat, yang menunjukkan stabilitas metabolik yang lebih baik pada pasien pneumonia dengan ventilasi mekanik, meskipun tidak ditemukan pengaruh bermakna terhadap NLR.

**Kata kunci:** Pneumonia; Nutrisi Enteral; Ventilasi Mekanik; Rasio Neutrofil terhadap Limfosit; Laktat

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## INTRODUCTION

Pneumonia remains one of the leading causes of morbidity and mortality worldwide, particularly among critically ill patients requiring intensive care and mechanical ventilation. According to the Global Burden of Disease 2021 report, lower respiratory tract infections continue to account for a substantial proportion of global infectious disease-related mortality.<sup>1</sup> In Indonesia, pneumonia also represents a major healthcare burden, especially among hospitalized and critically ill patients.<sup>2-4</sup> Previous studies conducted in tertiary referral centers have demonstrated considerable mortality rates among severe pneumonia patients admitted to intensive care units (ICUs).<sup>3,4</sup> Severe pneumonia requiring mechanical ventilation is characterized by dysregulated systemic inflammation, impaired tissue perfusion, and significant metabolic stress. Excessive inflammatory activation contributes to alveolar injury, impaired gas exchange, and progression toward respiratory failure and multiorgan dysfunction. In this context, simple and readily available biomarkers are clinically valuable for evaluating disease severity and treatment response.

The neutrophil-to-lymphocyte ratio (NLR) has emerged as an accessible inflammatory biomarker reflecting the balance between innate inflammatory activation and adaptive immune response. Elevated NLR values have been associated with increased disease severity, prolonged mechanical ventilation, and higher mortality among patients with pneumonia and sepsis.<sup>5-8</sup> Meanwhile, blood lactate level is a well-established marker of tissue hypoperfusion and metabolic dysfunction in critically ill patients. Persistent lactate elevation has consistently been associated with worse outcomes, including organ failure and mortality.<sup>6-8</sup>

Malnutrition and inadequate nutritional support further worsen outcomes in mechanically ventilated patients. Critically ill patients frequently experience hypercatabolism, increased energy expenditure, skeletal muscle

breakdown, and impaired immune function. Previous studies have reported malnutrition prevalence rates approaching 40–50% among ICU patients, particularly in those requiring prolonged ventilatory support.<sup>9-12</sup>

Pulmonary-specific enteral nutrition has been developed to address the unique metabolic and respiratory demands of critically ill patients with respiratory failure. These formulas generally contain lower carbohydrate and higher fat proportions, thereby reducing respiratory quotient and carbon dioxide production.<sup>13-16</sup> In addition, enrichment with omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) may provide anti-inflammatory and immunomodulatory effects.<sup>17-19</sup>

Several previous studies have demonstrated that pulmonary-specific nutritional formulas may improve oxygenation, reduce ventilatory demand, and support metabolic stability in critically ill patients.<sup>17-24</sup> Nevertheless, evidence regarding their effect on practical inflammatory and metabolic biomarkers, particularly NLR and blood lactate levels, remains limited. Furthermore, data from Indonesian critically ill populations are scarce.

Therefore, this study aimed to evaluate the effect of pulmonary-specific enteral nutrition on inflammatory and metabolic parameters, specifically NLR and blood lactate levels, in mechanically ventilated pneumonia patients.

## METHODS

### Study Design and Setting

This study was a double-blind randomized controlled trial with a parallel-group design conducted in the Intensive Care Unit (ICU) and High Care Unit (HCU) of a tertiary referral hospital in Jakarta, Indonesia, between January and December 2025.

### Participants

Adult patients aged 18–80 years with severe pneumonia requiring invasive mechanical ventilation were screened consecutively for eligibility. Pneumonia diagnosis was established

based on clinical presentation, radiological findings, and laboratory evaluation, and included community-acquired pneumonia, hospital-acquired pneumonia, and ventilator-associated pneumonia. Eligible participants were required to have anticipated tolerance for enteral feeding through a nasogastric or orogastric tube and to be hemodynamically stable at the time of enteral nutrition initiation. Patients were excluded if they were pregnant or lactating, had severe hepatic dysfunction, severe renal impairment defined as estimated glomerular filtration rate (eGFR)  $<15$  mL/min/1.73 m<sup>2</sup>, contraindications to enteral nutrition, gastrointestinal intolerance preventing enteral feeding, or refusal to participate in the study.

### **Randomization and Blinding**

Eligible patients were randomized in a 1:1 ratio using computer-generated block randomization. Double blinding was maintained by providing both enteral formulas in identical packaging. Investigators, treating physicians, nursing staff, and outcome assessors remained blinded to treatment allocation throughout the study period.

### **Intervention**

The intervention group received pulmonary-specific enteral nutrition (Pulmosol®), whereas the control group received standard hospital enteral nutrition. Both formulas were administered exclusively without combination with other enteral formulations. Energy requirements were determined using indirect calorimetry when available or estimated at 25–30 kcal/kg/day.<sup>15,16</sup> Enteral nutrition was initiated gradually, targeting approximately 70% of total energy expenditure during the first three days and advancing toward full caloric requirements thereafter. Protein intake targets ranged from 1.2 to 1.5 g/kg/day.<sup>11,15</sup>

### **Outcome Measures**

The primary outcome was the change in neutrophil-to-lymphocyte ratio (NLR), while the

secondary outcome was the change in blood lactate levels. Measurements were obtained on day 1 (baseline), day 3, and day 5 of observation.

### **Statistical Analysis**

Data analysis was performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean  $\pm$  standard deviation or median (interquartile range), depending on data distribution. Normality was assessed using the Shapiro–Wilk test. Repeated within-group comparisons were analyzed using the Friedman test. Between-group comparisons were performed using the independent t-test or Mann–Whitney U test, as appropriate. Categorical variables were analyzed using the chi-square test or Fisher’s exact test. A two-tailed p-value  $<0.05$  was considered statistically significant.

### **Ethical Considerations**

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Ethics Committee of the Faculty of Medicine, Universitas Indonesia–Cipto Mangunkusumo Hospital (Approval No. KET-1383/UN2.F1/ETIK/PPM.00.02/2023). Written informed consent was obtained from all participants or their legal representatives prior to study enrollment.

## **RESULTS**

### **Study Population and Baseline Characteristics**

This study included patients with pneumonia requiring mechanical ventilation who were admitted to the Intensive Care Unit (ICU) and High Care Unit (HCU) at Cipto Mangunkusumo National General Hospital. During the study period, a total of 59 patients were initially screened for eligibility. Of these, 3 patients were excluded due to failure to meet the inclusion criteria, consisting of hepatic dysfunction (n = 2) and severe renal impairment (n = 1).

A total of 56 eligible patients were subsequently randomized and equally allocated into two groups: the intervention group receiving a high-fat, low-carbohydrate enteral formula (n = 28) and the control group receiving a standard enteral formula (n = 28).

During follow-up, in the intervention group, 2 patients died and 2 required gastrointestinal surgery, preventing continuation of the intervention according to protocol. In the control group, 2 patients died, 1 required gastrointestinal surgery, and 3 required surgical procedures necessitating postponement or discontinuation of enteral nutrition.

Follow-up was conducted over 10 days, with daily clinical monitoring and laboratory assessments of neutrophil-to-lymphocyte ratio (NLR) and serum lactate measured during the early phase (1–48 hours), acute phase (days 3–7), and recovery phase (>7 days). At the end of the observation period, 24 patients in the intervention group and 22 patients in the control group were included in the final analysis.

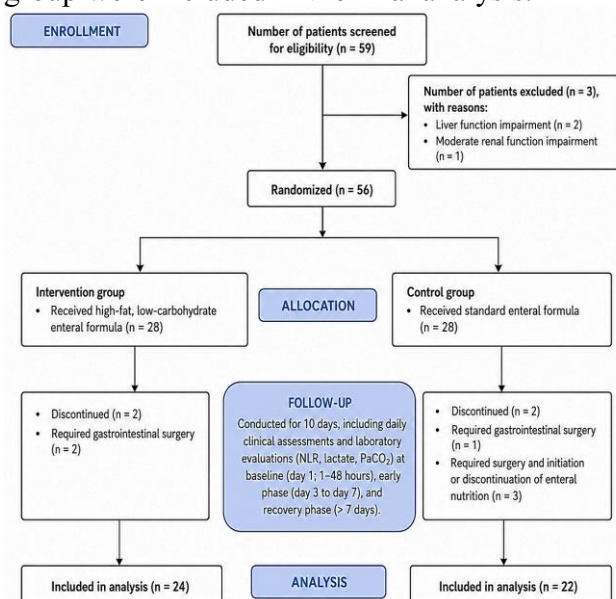


Figure 1. Study flow diagram of subject recruitment

A total of 56 subjects met the inclusion and exclusion criteria and were enrolled in the study, with 28 subjects allocated to each group. The mean age was  $46.46 \pm 17.96$  years in the intervention group and  $47.46 \pm 14.95$  years in

the control group, indicating comparable age distribution between groups. In terms of sex, the intervention group consisted of 13 males (46.4%) and 15 females (53.6%), while the control group included 10 males (35.7%) and 18 females (64.3%).

Most subjects had normal body mass index (BMI). In the intervention group, 60.7% were classified as normal weight, followed by underweight (35.7%) and overweight (3.6%), with no obese subjects identified. In the control group, 46.4% were classified as normal weight, followed by underweight (25.0%), overweight (10.7%), obesity class I (10.7%), and obesity class II (7.1%).

Assessment of disease severity using the APACHE II score showed that most subjects in both groups had moderate to severe illness. In the intervention group, 15 subjects (53.6%) were categorized as moderate, 11 (39.3%) as severe, and 2 (7.1%) as very severe. Similarly, in the control group, 12 subjects (50.0%) were categorized as moderate, 10 (41.7%) as severe, and 2 (8.3%) as very severe. Most subjects also had a Charlson Comorbidity Index (CCI) score  $\geq 3$ , accounting for 64.3% of the intervention group and 57.1% of the control group.

The mean daily caloric requirement was  $1787.6 \pm 253.0$  kcal in the intervention group and  $1709.9 \pm 291.3$  kcal in the control group. Median protein requirements were 61.7 (54.0–65.8) grams and 64.0 (53.0–68.6) grams, respectively. Mean carbohydrate requirements were  $265.0 \pm 52.7$  grams in the intervention group and  $251.5 \pm 59.0$  grams in the control group, while median fat requirements were 49.4 (42.0–52.0) grams and 46.0 (41.5–52.0) grams, respectively. The complete distribution of baseline characteristics between groups is presented in Table 1.

Table 1. Baseline characteristics of study subjects

Characteristic	Group	
	Intervention (N=28)	Control (N=28)
Age, mean $\pm$ SD	46,46 (17,96)	47,46 (14,95)
Sex, n (%)		
Male	13 (46,4)	10 (35,7)
Female	15 (53,6)	18 (64,3)
Body Mass Index, n (%)		

Underweight	10 (35,7)	7 (25,0)
Normal	17 (60,7)	13 (46,4)
Overweight	1 (3,6)	3 (10,)
Class I Obesity	0 (0,0)	3 (10,7)
Class II Obesity	0 (0,0)	2 (7,1)
Charlson Comorbidity Index, n (%)		
<3	10 (35,7)	8 (33,3)
≥3	18 (64,3)	16 (66,7)
APACHE II score, n (%)		
Moderate (11–19)	15 (53,6)	12 (50,0)
Severe (20–29)	11 (39,3)	10 (41,7)
Very severe (≥30)	2 (7,1)	2 (8,3)
Daily caloric requirement (kcal), mean ± SD	1787,6 ± 253,0	1709,9 ± 291,3
Protein requirement (g), median (IQR)	61,7 (54,0–65,8)	64,0 (53,0–68,6)
Carbohydrate requirement (g), mean ± SD	265,0 ± 52,7	251,5 ± 59,0
Fat requirement (g), mean ± SD	49,4 (42,0–52,0)	46,0 (41,5–52,0)

### Baseline Inflammatory and Perfusion Parameters

Baseline inflammatory and tissue perfusion parameters were not normally distributed and are therefore presented as median and interquartile range (IQR). Baseline analyses in this section included all randomized subjects, whereas repeated-measures analyses included only subjects with complete serial measurements. The median NLR on day 1 was 10.42 (IQR 5.43–16.19) in the intervention group and 11.69 (IQR 7.15–18.29) in the control group. The median serum lactate level on day 1 was 2.25 mmol/L (IQR 1.13–3.20) in the intervention group and 2.55 mmol/L (IQR 1.43–3.55) in the control group. A summary of baseline inflammatory and perfusion parameters is presented in Table 2.

**Table 2. Baseline inflammatory and perfusion parameters of study subjects**

Characteristics	Intervention Group (N=24)	Control Group (N=22)
Day-1 NLR, median (IQR)	10,42 (5,43 – 16,19)	11,69 (7,15 – 18,29)
Day-1 Lactate (mmol/L), median (IQR)	2,25 (1,13 – 3,2)	2,55 (1,43 – 3,55)

### Changes in Inflammatory Parameters During Observation

Changes in NLR and lactate levels on days 1, 3, and 5 were analyzed using the Friedman test due to non-normal distribution and repeated measurements. Repeated-measures

analyses included only subjects with complete serial measurements, consisting of 24 subjects in the intervention group and 22 subjects in the control group.

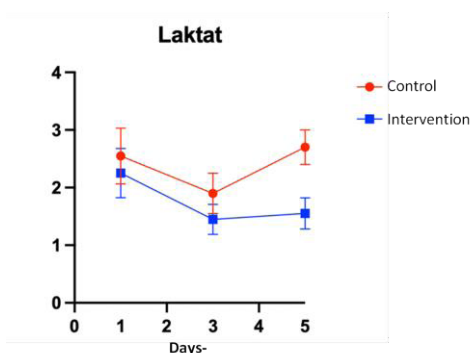
In the intervention group, no significant change in NLR was observed during the observation period ( $p = 0.276$ ). In contrast, the control group showed a significant change in NLR over time ( $p = 0.010$ ).

For lactate levels, both groups demonstrated significant changes during follow-up. The intervention group showed a significant reduction in lactate levels over time ( $p = 0.004$ ), while the control group also demonstrated significant changes ( $p = 0.020$ ). Descriptively, lactate levels in the intervention group decreased from day 1 to day 3 and remained relatively stable until day 5. In contrast, the control group showed a decrease on day 3 followed by an increase on day 5.

A summary of changes in inflammatory and tissue perfusion parameters during the observation period is presented in Table 3.

**Table 3. Changes in inflammatory parameters during the observation period within each group**

Parameter	Intervention Group (N=24)	Control Group (N=22)
<b>NLR, median (IQR)</b>		
Day 1	11,25 (6,66 – 15,67)	12,19 (8,09 – 18,77)
Day 3	10,60 (7,86 – 18,86)	11,78 (7,90 – 19,70)
Day 5	8,18 (6,99 – 22,19)	9,98 (5,80 – 18,40)
<b>Lactate (mmol/L), median (IQR)</b>		
Day 1	2,25 (1,10 – 3,20)	2,55 (1,40 – 3,60)
Day 3	1,45 (0,90 – 2,15)	1,90 (1,50 – 3,00)
Day 5	1,55 (0,95 – 2,20)	2,70 (2,30 – 3,60)



**Figure 2. Changes in NLR in the intervention and control groups from day 1 to day 5**

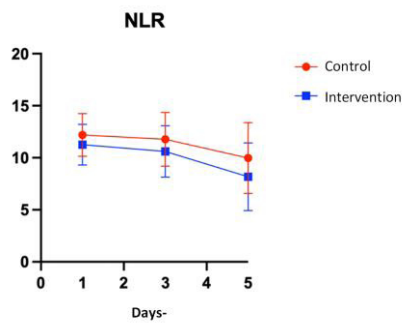


Figure 3. Changes in serum lactate levels in the intervention and control groups from day 1 to day 5

### Between-Group Comparison of Parameter Changes

Between-group comparisons of biomarker changes were analyzed using the Mann–Whitney U test. No significant differences were observed in NLR changes between the intervention and control groups during the intervals of day 1–3 ( $p = 0.775$ ), day 3–5 ( $p = 0.126$ ), or cumulative day 1–5 changes ( $p = 0.676$ ). In contrast, lactate changes demonstrated significant differences between groups during the interval of day 3–5 ( $p = 0.017$ ) and cumulative day 1–5 changes ( $p = 0.037$ ). During the day 3–5 interval, the control group demonstrated an increase in lactate levels, whereas the intervention group remained relatively stable. Overall, the intervention group demonstrated a trend toward lactate reduction over time, whereas the control group did not show a consistent downward pattern. A summary of between-group comparisons is presented in Table 4.

Table 4. Comparison of changes ( $\Delta$ ) in inflammatory parameters between groups

Characteristics	Intervention Group (N=24)	Control Group (N=22)	p-value
<b>NLR</b>			
$\Delta 1-3$	-1,43 (-3,17 – 9,63)	-1,33 (-3,85 – 7,22)	0,775
$\Delta 3-5$	0,35 (-3,15 – 8,29)	-1,90 (-5,06 – -0,87)	0,126
$\Delta 1-5$	-1,66 (-5,66 – 9,10)	-1,48 (-4,92 – 7,05)	0,676
<b>Lactate (mmol/L)</b>			
$\Delta 1-3$	-0,75 (-1,05 – 0,05)	-0,75 (-1,40 – -0,40)	0,749
$\Delta 3-5$	-0,10 (-0,35 – 0,70)	0,95 (0,50 – 1,30)	<b>0,017</b>
$\Delta 1-5$	-0,25 (-1,15 – 0,00)	0,20 (-0,60 – 1,00)	<b>0,037</b>

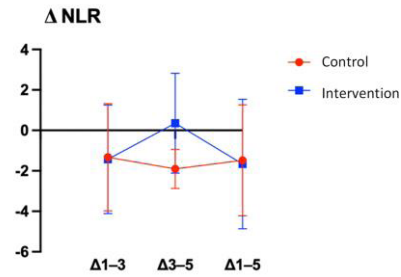


Figure 4. Comparison of changes in Neutrophil-to-Lymphocyte Ratio ( $\Delta$ NLR) between the intervention and control groups

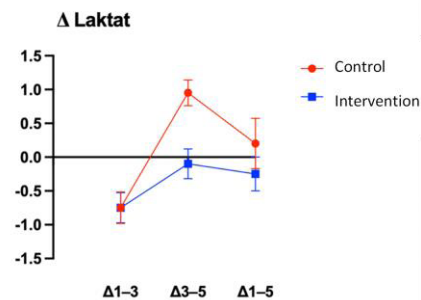


Figure 5. Comparison of changes in lactate levels ( $\Delta$ Lactate) between the intervention and control groups

### DISCUSSION

This randomized controlled trial evaluated the effect of pulmonary-specific enteral nutrition on inflammatory and metabolic parameters in mechanically ventilated patients with pneumonia. The principal finding of this study was that pulmonary-specific enteral nutrition was associated with more favorable lactate dynamics during the observation period, whereas no significant effect was observed on neutrophil-to-lymphocyte ratio (NLR).<sup>22–24</sup>

The absence of significant differences in NLR between groups suggests that short-term nutritional intervention alone may not be sufficient to substantially modify systemic inflammatory responses in critically ill pneumonia patients. In severe infection, inflammatory activation is highly complex and influenced by multiple factors, including infection severity, underlying comorbidities,

corticosteroid exposure, organ dysfunction, and physiologic stress response. NLR reflects the dynamic balance between neutrophil-mediated innate immune activation and lymphocyte suppression, both of which may fluctuate considerably during critical illness. Previous studies have consistently demonstrated that elevated NLR is associated with poor clinical outcomes in pneumonia and sepsis; however, its responsiveness to nutritional intervention remains less clearly established<sup>5,6,25-27</sup>

Although pulmonary-specific enteral formulas are enriched with omega-3 fatty acids that possess anti-inflammatory properties, the relatively short duration of observation in this study may have limited the ability to detect measurable changes in inflammatory biomarkers. In critically ill patients, modulation of systemic inflammation often requires sustained intervention and may not be adequately reflected by early changes in hematologic indices alone. Moreover, NLR itself is influenced by numerous concurrent ICU-related factors, including secondary infection, adrenergic response, medication exposure, and corticosteroid administration, which may further obscure the isolated effect of nutritional therapy<sup>17-19,25</sup>

The differing responses observed between lactate and NLR may reflect the distinct biological pathways represented by these biomarkers. Lactate is closely associated with tissue perfusion, oxygen utilization, and metabolic adaptation, which may respond more rapidly to alterations in substrate composition and energy metabolism. In contrast, NLR reflects systemic immune and inflammatory regulation, which is considerably more complex and may require longer periods of intervention before meaningful changes become apparent. This discrepancy suggests that metabolic improvement may precede measurable modulation of systemic inflammatory responses during critical illness.

In contrast to NLR, blood lactate demonstrated a more clinically meaningful pattern throughout the study period. Patients

receiving pulmonary-specific enteral nutrition showed a gradual reduction and subsequent stabilization of lactate levels, whereas the control group demonstrated more fluctuating lactate trajectories, including a rebound increase toward day 5. Although the magnitude of change was relatively modest, these findings may indicate improved metabolic adaptation among patients receiving pulmonary-specific enteral nutrition<sup>20,21</sup>

Lactate is widely recognized as an important biomarker of tissue hypoperfusion, impaired oxygen utilization, and metabolic stress in critically ill patients. Persistent elevation of lactate has consistently been associated with worse outcomes, including multiorgan dysfunction and mortality. Therefore, improvement in lactate dynamics may reflect better tissue oxygenation, enhanced cellular metabolism, and improved physiologic recovery. Even small improvements in lactate trajectory may still be clinically relevant in critically ill patients, considering the established association between persistent hyperlactatemia and adverse outcomes in the intensive care setting.<sup>20,21</sup>

Several mechanisms may explain the more favorable lactate profile observed in the intervention group. Pulmonary-specific enteral nutrition is characterized by lower carbohydrate and higher fat composition, resulting in a lower respiratory quotient and reduced carbon dioxide production. Reduced carbon dioxide generation may lessen ventilatory burden and improve respiratory efficiency in mechanically ventilated patients. In addition, omega-3 fatty acids such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) possess anti-inflammatory and endothelial-stabilizing properties that may contribute to improved microcirculatory perfusion and cellular oxygen utilization.<sup>17-19</sup> Together, these mechanisms may partially explain the improved metabolic stability observed in the intervention group.<sup>13-19</sup>

Our findings are generally consistent with previous studies demonstrating potential metabolic and respiratory benefits of specialized enteral nutrition in critically ill patients. Prior

investigations have reported that pulmonary-oriented nutritional strategies may improve oxygenation parameters, reduce ventilatory demand, and support metabolic recovery, particularly among mechanically ventilated patients.<sup>22-24</sup> Nevertheless, evidence regarding their direct effect on inflammatory biomarkers remains inconsistent, highlighting the multifactorial nature of systemic inflammation during critical illness.<sup>17,18,22</sup>

From a clinical perspective, these findings suggest that pulmonary-specific enteral nutrition may provide additional metabolic support in mechanically ventilated pneumonia patients, particularly in maintaining metabolic stability during the acute phase of illness. Although the intervention did not significantly alter inflammatory markers, the observed improvement in lactate trajectory may still carry clinical relevance, considering that lactate measurement is routinely available and widely utilized in ICU practice.<sup>20,21</sup> These findings may also suggest that the primary short-term benefit of pulmonary-specific enteral nutrition lies more in metabolic optimization rather than direct suppression of systemic inflammation.

Several limitations of this study should be acknowledged. First, the relatively small sample size may have limited the statistical power to detect subtle differences in inflammatory parameters such as NLR. Second, this was a single-center study conducted in a tertiary referral hospital, which may limit generalizability to other settings. Third, several potentially important confounding factors, including antibiotic regimens, corticosteroid administration, and ventilatory management strategies, were not fully standardized during the study period. Fourth, inflammatory assessment in this study relied primarily on NLR, which

represents an indirect hematologic marker of inflammation. More specific inflammatory biomarkers such as C-reactive protein, interleukin-6, or procalcitonin were not evaluated and may have provided a more comprehensive assessment of inflammatory modulation. Finally, the relatively short duration of observation precluded assessment of longer-term clinical outcomes such as mortality, duration of mechanical ventilation, and ICU length of stay.

Despite these limitations, this study provides important local evidence regarding pulmonary-specific enteral nutrition in critically ill pneumonia patients and contributes to the still-limited literature evaluating metabolic-oriented nutritional strategies in mechanically ventilated populations.<sup>22-24</sup> Future multicenter studies with larger sample sizes and longer follow-up duration are needed to determine whether improvements in metabolic parameters may translate into meaningful clinical outcomes, including ventilator-free days, ICU length of stay, and mortality reduction.

## CONCLUSION

Pulmonary-specific enteral nutrition was associated with more favorable lactate dynamics, suggesting improved metabolic stability in mechanically ventilated pneumonia patients, although no significant effect on neutrophil-to-lymphocyte ratio was observed. These findings support the potential role of pulmonary-specific enteral nutrition as an adjunctive metabolic strategy in critically ill pneumonia patients. Further multicenter studies with larger sample sizes and longer follow-up are needed to evaluate its impact on inflammatory responses and clinically relevant outcomes.

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