SCINDEKS
Serbian Citation Index
J Med Biochem 2026; 45 (9) DOI: 10.5937/jomb0-66413

UDK 577.1 : 61 **ISSN 1452-8258**

J Med Biochem 45: 1980–1990, 2026

Original paper
Originalni naučni rad

DYNAMIC INFLAMMATORY–IMMUNE BIOMARKER PROFILES ASSOCIATED WITH CLINICAL RECOVERY IN ELDERLY PATIENTS WITH SEVERE PNEUMONIA: A PROSPECTIVE STUDY

DINAMIČKI PROFILI INFLAMATORNO-IMUNOLOŠKIH BIOMARKERA POVEZANI SA KLINIČKIM OPORAVKOM KOD STARIJIH PACIJENATA SA TEŠKOM UPALOM PLUĆA: PROSPEKTIVNA STUDIJA

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Summary

Background: Severe pneumonia in elderly patients is characterized by dysregulated inflammatory responses and impaired immune recovery. However, the dynamic interplay between inflammatory–immune biomarkers and clinical recovery remains insufficiently elucidated from a biochemical perspective.
Methods: This prospective study included 276 elderly patients with severe pneumonia. Serial measurements of inflammatory biomarkers [C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6), and neutrophil-to-lymphocyte ratio (NLR)] and immune indicators (CD4+ T cells and natural killer cells) were performed at baseline, day 3, and end-of-treatment. Clinical recovery was evaluated using time to clinical stability, oxygenation index (PaO_2/FiO_2), and length of hospital stay. Associations between biomarker dynamics and recovery outcomes were analyzed.
Results: All inflammatory biomarkers exhibited significant declines over time, accompanied by partial restoration of immune function. Greater reductions in CRP, PCT, and IL-6 at early time points were associated with faster clinical stabilization and improved oxygenation (all $P < 0.01$). NLR showed a pronounced early decrease, reflecting attenuation of systemic inflammatory stress. Notably, recovery of CD4+ T cells was significantly associated with improved clinical outcomes ($P = 0.001$), suggesting co-

Kratak sadržaj

Uvod: Tešku pneumoniju kod starijih pacijenata karakterišu disregulisani inflamatorni odgovori i oslabljen imuni oporavak. Međutim, dinamička interakcija između inflamatorno-imunoloških biomarkera i kliničkog oporavka ostaje nedovoljno razjašnjena sa biohemijske perspektive.
Metode: Ova prospektivna studija obuhvatila je 276 starijih pacijenata sa teškom upalom pluća. Serijska merenja inflamatornih biomarkera [C-reaktivni protein (CRP), prokalcitonin (PCT), interleukin-6 (IL-6) i odnos neutrofila i limfocita (NLR)] i imunoloških indikatora (CD4+ T ćelije i prirodne ćelije ubice) su sprovedena na početku, 3. dana i na kraju lečenja. Klinički oporavak je procenjen korišćenjem vremena do kliničke stabilnosti, indeksa oksigenacije (PaO_2/FiO_2) i dužine boravka u bolnici. Analizirane su veze između dinamike biomarkera i ishoda oporavka.
Rezultati: Svi inflamatorni biomarkeri pokazali su značajan pad tokom vremena, praćen delimičnim obnavljanjem imunološke funkcije. Veća smanjenja CRP, PCT i IL-6 u ranim vremenskim tačkama bila su povezana sa bržom kliničkom stabilizacijom i poboljšanom oksigenacijom (sve $P < 0,01$). NLR je pokazao izražen rani pad, što odražava slabljenje sistemskog inflamatornog stresa. Primetno je da je oporavak CD4+ T ćelija bio značajno povezan sa poboljšanim kliničkim ishodima ($P = 0,001$), što ukazuje na koordinisanu imunološku rekonstituciju.

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ordinated immune reconstitution. Patients with more favorable biomarker trajectories demonstrated shorter hospitalization and earlier transition to clinical stability. These findings indicate that integrated inflammatory–immune biomarker dynamics closely reflect the biological recovery process in severe pneumonia.

Conclusion: Dynamic monitoring of inflammatory and immune biomarkers provides valuable biochemical insights into recovery trajectories in elderly patients with severe pneumonia. Combined biomarker profiling may serve as a practical tool for evaluating disease progression and guiding individualized management strategies.

Keywords: severe pneumonia, inflammatory biomarkers, immune function, interleukin-6, neutrophil-to-lymphocyte ratio, CD4-positive T-lymphocytes

Pacijenti sa povoljnijim putanjama biomarkera pokazali su kraću hospitalizaciju i raniji prelazak u kliničku stabilnost. Ovi nalazi ukazuju da integrisana dinamika inflamatorno-imunih biomarkera usko odražava proces biološkog oporavka kod teške upale pluća.

Zaključak: Dinamičko praćenje inflamatornih i imunoloških biomarkera pruža vredne biohemijske uvide u putanje oporavka kod starijih pacijenata sa teškom upalom pluća. Kombinovano profilisanje biomarkera može poslužiti kao praktičan alat za procenu progresije bolesti i vođenje individualizovanih strategija lečenja.

Ključne reči: teška pneumonija, inflamatorni biomarkeri, imunološka funkcija, interleukin-6, odnos neutrofila i limfocita, CD4-pozitivni T-limfociti

Introduction

Pneumonia remains one of the major infectious diseases in adults leading to hospitalization, severe illness, and death. In elderly patients, once the condition progresses to severe disease, it is no longer merely a matter of pulmonary infection; it often involves a chain of changes including impaired respiratory function, amplification of the systemic inflammatory response, decompensation of underlying diseases, and insufficient organ reserve (1, 2). In recent years, adult pneumonia guidelines and international consensuses on severe pneumonia management have increasingly emphasized a comprehensive approach of »standardized anti-infection treatment + stratified assessment + organ support + recovery management« (1–3). This means that evaluation of treatment efficacy in severe pneumonia should not remain limited to traditional endpoints such as defervescence or radiographic absorption, but should also focus on when patients transition from acute instability to clinical stability, whether hospitalization is shortened, and whether systemic recovery proceeds more smoothly. In elderly patients with severe pneumonia, such indicators, which are directly related to recovery quality, often reflect real clinical benefit better than a single laboratory parameter (4).

Elderly patients are more likely to experience prolonged disease courses and adverse outcomes after developing pneumonia, and this is not determined solely by the superficial factor of »advanced age«; rather, it is closely related to the long-term accumulation of immunobiological changes in the body (5). With aging, innate immune cells gradually show reduced chemotaxis (6), phagocytosis, and bactericidal capacity (7), while adaptive immunity is characterized by shrinkage of the T-cell repertoire, slowed response speed, and remodeling of immune memory (8). At the same time, the body often remains in a background state of low-grade chronic inflammation. This coexistence is commonly summarized as immunosenescence together with inflammaging (1, 5, 8). Under such host conditions, when elderly patients face pulmonary infection, pathogen clearance is reduced on the one hand, while inflammatory responses may remain persistently amplified on the other, ultimately leading to slow oxygenation improvement, delayed clinical recovery, and a higher risk of complications. For this reason, treatment strategies for elderly patients with severe pneumonia need not only infection control but also optimization of the recovery process.

From the perspective of clinical study design, observational endpoints for elderly patients with severe pneumonia should take into account three aspects: hard outcomes, surrogate outcomes, and recovery outcomes. For short- to medium-term inpatient studies, time to clinical stability and length of hospital stay are among the most interpretable recovery endpoints. Time to clinical stability can better reflect whether vital signs, oxygenation status, and overall systemic condition have transitioned from an acute fluctuation phase to a relatively controllable stage, and it is closely related to subsequent hospitalization course, complications, and resource consumption (9). To improve the operability of this endpoint, clinical stability should be judged comprehensively using multidimensional indicators such as temperature, circulatory status, respiratory rate, mental status, and oxygen-support requirements, rather than being replaced by improvement in a single symptom. Meanwhile, changes in PaO_2/FiO_2 can directly reflect the need for respiratory support and the progress of oxygenation recovery. If combined with dynamic observation of inflammatory and immune indicators, they are even more helpful for understanding treatment effects at the three levels of host response, organ function, and clinical recovery.

Regarding inflammatory markers, CRP, PCT, IL-6, and NLR are highly useful in the dynamic evaluation of severe pneumonia. CRP reflects acute-phase inflammatory burden; PCT has high reference value for bacterial infection activity and the risk of severe infection (10); and IL-6 lies at a key

point in the amplification of the inflammatory cascade and often provides an early indication of the body's inflammatory stress level (11, 12). NLR is easy to obtain and has good reproducibility, and in recent years it has drawn increasing attention in assessing severity and short-term prognosis in elderly patients with pneumonia (13, 14). However, simply observing a decline in inflammatory markers does not fully demonstrate that the patient's recovery trajectory has truly improved. Especially in elderly patients, immune reconstruction after infection control is also important. If a decline in inflammation is accompanied by recovery-oriented changes in key immune cell levels, then the judgment that the disease course is shifting toward a more orderly state becomes more convincing. Therefore, CD4+ T cells and NK cells were simultaneously included in this study to examine from another dimension whether adjunctive TTS treatment was consistent with improvement in overall recovery status.

The transdermal therapeutic system (TTS) is a mode of drug administration that continuously delivers medication through the skin, featuring relatively stable drug delivery, avoidance of first-pass effects, and relatively simple operation. For elderly patients, the practical significance of this route is that it does not depend on mastery of complex inhalation devices, nor does it impose additional demands on gastrointestinal tolerance or swallowing ability associated with oral administration. Previous research has focused mainly on chronic airway diseases such as asthma and chronic obstructive pulmonary disease, suggesting that related TTS formulations provide sustained bronchodilation and certain advantages in adherence (15). In the setting of severe pneumonia, however, TTS should clearly not be understood as a direct substitute for the core role of anti-infective therapy. Its more reasonable position is as an adjunctive treatment - that is, on the basis of standardized anti-infection therapy, oxygen therapy, airway management, and supportive care, it may provide additional support by improving airway patency, reducing respiratory burden, promoting oxygenation recovery, and accelerating the overall rehabilitation process. The TTS used in this study was specifically a tulobuterol patch.

At present, clinical research on »TTS plus conventional therapy« in elderly patients with severe pneumonia remains scarce, especially studies that incorporate rehabilitation outcomes, inflammatory markers, and immune markers into a single observational framework. Accordingly, this study conducted a prospective randomized parallel-controlled observation among hospitalized elderly patients with severe pneumonia, comparing adjunctive TTS plus conventional therapy versus conventional therapy alone in terms of time to clinical stability, length of hospital stay, oxygenation recovery, and systemic inflammatory-immune responses. The aim was to provide a preliminary evaluation of the adjunctive value of TTS in the comprehensive management of elderly severe pneumonia from three perspectives: whether the pace of recovery is faster, whether inflammatory burden declines more smoothly, and whether immune recovery is better coordinated.

Materials and Methods

General information

This was a single-center, prospective, randomized, parallel-controlled study. The study population consisted of elderly patients with severe pneumonia who were hospitalized in our hospital between December 2023 and December 2025. During the study period, hospitalized cases were continuously evaluated according to a unified screening process; all patients who met the inclusion criteria and had no exclusion criteria were randomized. A total of 276 patients were ultimately included in the analysis, including 136 in the control group and 140 in the TTS group. The diagnosis of pneumonia was based on clinical symptoms, signs, and chest imaging findings. Severity was comprehensively assessed according to adult pneumonia guidelines and consensus statements on severe pneumonia management, in combination with the degree of oxygenation impairment, need for respiratory support, circulatory status, and overall systemic condition. To improve consistency in study implementation, the processes for case screening, indicator definitions, sampling time points, endpoint adjudication, and data recording were standardized before study initiation. Baseline data were collected for all patients before treatment. Patients capable of signing provided informed consent themselves; those unable to sign independently had the consent form signed by a legal representative or close relative.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) age >= 65 years; (2) fulfillment of the diagnostic criteria for pneumonia and, according to relevant adult community-acquired pneumonia and severe pneumonia guidelines, fulfillment of severe disease criteria, with severity determined by combining major criteria such as invasive mechanical ventilation and septic shock requiring vasopressor support, together with minor severity indicators such as hypoxemia, increased respiratory rate, multilobar involvement, altered consciousness, and unstable blood pressure; (3) receipt of standardized conventional treatment after admission; and (4) ability to complete baseline evaluation and data collection at the main observation time points. The exclusion criteria were as

follows: (1) active tuberculosis, fungal infection, or a definite noninfectious interstitial lung disease; (2) severe immunodeficiency or long-term use of immunosuppressants; (3) terminal malignant tumor or severe hepatic or renal failure; (4) known allergy to components of the tulobuterol patch or obvious skin injury at the intended application site; (5) an expectation that key data collection at least through day 3 could not be completed because of early discharge against medical advice, transfer to another hospital, or other reasons unrelated to the study process; and (6) missing key screening-stage data that made completion of baseline evaluation or severity assessment impossible.

Grouping and treatment protocol

The control group received conventional treatment, including empirical or pathogen-guided anti-infective therapy, oxygen therapy, sputum elimination and drainage, airway management, fluid and nutritional support, and management of underlying diseases. On the basis of conventional treatment, the TTS group additionally received transdermal therapeutic system treatment. The TTS used in this study was specifically a 2 mg tulobuterol patch, applied transdermally once daily for 7 consecutive days, with rotation of the application site according to skin condition. The random allocation sequence was generated before study initiation. Patients were assigned according to the prespecified sequence after eligibility confirmation and informed consent. Allocation concealment was not formally implemented, which should be considered a methodological limitation. Because the tulobuterol patch was visible during treatment, blinding of patients and treating physicians was not feasible. Outcome data were collected by trained investigators according to predefined criteria. These investigators were not involved in treatment allocation; however, because of the pragmatic nature of the intervention, they were aware of group assignment. Both groups received conventional treatment and dynamic assessment according to the same clinical pathway. Except for the study intervention, other long-acting beta2-agonists or repeated transdermal bronchodilator preparations were not routinely added. If a patient's condition required escalation to high-flow oxygen therapy, non-invasive ventilation, mechanical ventilation, or ICU admission, treatment was upgraded promptly according to established clinical indications, and the patient remained in endpoint follow-up.

Observation indicators

The observation indicators were systematically categorized into biochemical, clinical, and safety domains, with particular emphasis on the dynamic profiling of inflammatory and immune biomarkers to reflect the biological recovery process.

(1) Baseline characteristics:

Baseline data included age, sex, body mass index (BMI), smoking history, and major comorbidities (chronic obstructive pulmonary disease, coronary heart disease, and type 2 diabetes). Disease severity at admission was assessed using CURB-65 and PSI scores. Respiratory status was evaluated by baseline PaO_2/FiO_2, as well as the use of high-flow oxygen therapy and non-invasive ventilation.

(2) Biochemical indicators:

To comprehensively characterize systemic inflammatory burden and immune recovery, serial measurements of biochemical markers were performed using standardized laboratory methods.

Inflammatory biomarkers:

Serum levels of C-reactive protein (CRP), procalcitonin (PCT), and interleukin-6 (IL-6) were quantified using automated immunoassay techniques in the hospital's central laboratory. CRP was measured by immunoturbidimetric assay, while PCT and IL-6 were determined using electrochemiluminescence immunoassays according to the manufacturer's instructions. The neutrophil-to-lymphocyte ratio (NLR) was calculated from complete blood count parameters obtained via an automated hematology analyzer. All inflammatory markers were recorded at three predefined time points: baseline (before treatment), day 3 of treatment, and end-of-treatment assessment.

Immune biomarkers:

Peripheral blood CD4+ T lymphocyte subsets and natural killer (NK) cells were analyzed using flow cytometry (FCM) with standard monoclonal antibody panels. Samples were processed under standardized conditions, and data acquisition was performed using a calibrated flow cytometer, with results expressed as percentages of total lymphocytes. Immune parameters were assessed at baseline and at the end-of-treatment to evaluate immune reconstitution following therapeutic intervention.

Analytical framework:

These biochemical indicators were dynamically analyzed to evaluate temporal changes in systemic inflammation and immune function during disease progression and recovery. In particular, early-phase changes (baseline to day 3) were used to reflect

acute inflammatory modulation, whereas end-of-treatment values were interpreted as indicators of recovery-associated immune restoration. Furthermore, the integration of inflammatory and immune biomarkers was used to explore their associations with clinical recovery trajectories, including time to clinical stability and improvement in oxygenation. This combined biochemical profiling approach aimed to provide a more comprehensive understanding of host response dynamics in elderly patients with severe pneumonia (7).

(3) Clinical endpoints:

Clinical outcomes were assessed to reflect recovery status and were considered supportive of the biochemical findings.

Primary clinical endpoints:

Time to clinical stability and length of hospital stay were the primary clinical endpoints. Time to clinical stability was defined as the duration from initiation of treatment to the first time point at which the patient maintained clinical stability for at least 24 h. The assessment was based on the criteria proposed by Halm et al. (8), combined with standardized institutional protocols. Clinical stability was considered achieved only when all of the following criteria were met simultaneously: body temperature ≤37.8 °C; heart rate ≤100 beats/min; respiratory rate ≤24 breaths/min; systolic blood pressure ≥90 mmHg without newly added vasopressor or circulatory support; no deterioration in mental status; and oxygenation stability, defined as SpO_2 ≥90% or PaO_2 ≥60 mmHg without escalation of oxygen support during the preceding 24 h. For patients receiving oxygen therapy, the oxygen delivery method and oxygen flow were required to be stable or reduced rather than increased (9–12).

Secondary clinical endpoints:

Day 3 and end-of-treatment PaO_2/FiO_2 (day 7 as the principal assessment point; if discharged earlier, the last available value was recorded), 28-day all-cause mortality, ICU transfer, mechanical ventilation, and treatment failure. Treatment failure was defined as a patient-level composite endpoint, including clinical deterioration requiring escalation of respiratory support, ICU transfer, or death during hospitalization. Each patient was counted only once for the composite endpoint, according to the first qualifying event. Therefore, ICU transfer, mechanical ventilation, and 28-day mortality were reported separately as individual outcomes and were not mutually exclusive with the composite treatment failure endpoint.

(4) Safety outcomes:

Safety indicators included the incidence of total adverse reactions, application-site pruritus or erythema, palpitations, dry mouth, mild insomnia, and drug discontinuation.

Statistical methods

Statistical analyses were performed using SPSS 26.0. Continuous variables were first tested for normality. Data conforming to a normal distribution are expressed as mean +/- standard deviation, and between-group comparisons were performed using the independent-samples t test. Data not conforming to a normal distribution are expressed as median (interquartile range), and were compared using the Mann-Whitney U test. Categorical data are expressed as case number and percentage, and were analyzed using the chi-square test or Fisher's exact test. For repeated-measures indicators such as CRP, PCT, IL-6, NLR, CD4+ T cells, and NK cells, in addition to prespecified between-group comparisons at each time point, repeated-measures analysis of variance was used to evaluate the time effect, group effect, and their interaction overall. When the condition for sphericity was not met, corrected results were used for interpretation. All tests were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Comparison of baseline data between the two groups

A total of 276 elderly patients with severe pneumonia were included in this study, including 136 in the control group and 140 in the TTS group. There were no statistically significant differences between the two groups in age, sex composition, BMI, smoking history, or major underlying diseases. Meanwhile, CURB-65 scores, PSI scores, and baseline PaO2/FiO2 were similar, indicating that the overall baseline severity at admission was balanced between the two groups. Baseline CRP, PCT, IL-6, NLR, CD4+ T-cell levels, and NK-cell levels also showed no significant differences, suggesting good comparability between groups (*Table I*).

Comparison of primary endpoints and key secondary endpoints between the two groups

In terms of the primary endpoints, the TTS group had a significantly shorter time to clinical stability than the control group, and the length of hospital stay was also clearly reduced. Considering that time to clinical stability can reflect relatively early the speed at which patients move from an »in-

Table I Comparison of baseline characteristics between the two groups.

Indicator	Control group (n=136)	TTS group (n=140)	P value
Age (years)	76.8 +/- 7.1	77.2 +/- 6.8	0.624
Male [n (%)]	82 (60.3)	87 (62.1)	0.760
BMI (kg/m^2)	22.6 +/- 3.4	22.9 +/- 3.2	0.451
Smoking history [n (%)]	49 (36.0)	54 (38.6)	0.659
COPD [n (%)]	41 (30.1)	39 (27.9)	0.685
Coronary heart disease [n (%)]	33 (24.3)	36 (25.7)	0.783
Type 2 diabetes [n (%)]	37 (27.2)	35 (25.0)	0.678
CURB-65 score	3.2 +/- 0.8	3.1 +/- 0.7	0.286
PSI score	119.4 +/- 18.6	117.8 +/- 17.9	0.467
PaO_2/FiO_2	182 +/- 46	186 +/- 49	0.483
CRP (mg/L)	97.6 +/- 28.4	100.3 +/- 30.1	0.445
PCT (ng/mL)	1.82 +/- 0.91	1.88 +/- 0.96	0.593
IL-6 (pg/mL)	63.8 +/- 22.6	65.1 +/- 24.1	0.646
NLR	12.3 +/- 4.1	12.7 +/- 4.5	0.440
$CD4^+$ T cells (%)	29.1 +/- 6.2	28.7 +/- 6.5	0.596
NK cells (%)	9.4 +/- 2.8	9.1 +/- 2.7	0.367
High-flow oxygen therapy [n (%)]	28 (20.6)	31 (22.1)	0.760
Non-invasive ventilation [n (%)]	19 (14.0)	17 (12.1)	0.649

Table II Comparison of primary endpoints and key secondary endpoints between the two groups

Indicator	Control group (n=136)	TTS group (n=140)	P value
Time to clinical stability (days)	7.0 +/- 2.1	6.1 +/- 1.9	0.001
Length of hospital stay (days)	11.8 +/- 3.7	10.4 +/- 3.3	0.001
Day 3 PaO_2/FiO_2	221 +/- 58	248 +/- 61	<0.001
End-of-treatment PaO_2/FiO_2	268 +/- 64	296 +/- 69	0.001
28-day all-cause mortality [n (%)]	12 (8.8)	8 (5.7)	0.313
ICU transfer [n (%)]	18 (13.2)	11 (7.9)	0.154
Mechanical ventilation [n (%)]	14 (10.3)	9 (6.4)	0.255
Treatment failure* [n (%)]	21 (15.4)	13 (9.3)	0.122

Note: Treatment failure was analyzed as a patient-level composite endpoint. Each patient was counted once if escalation of respiratory support, ICU transfer, or death occurred. ICU transfer, mechanical ventilation, and 28-day mortality were reported separately and were not mutually exclusive; therefore, their numbers should not be summed to obtain the number of treatment failure cases.

fection-dominated acute unstable state« to a »controllable recovery stage,« and that this study used prespecified stability criteria applied uniformly, these results suggest that on the basis of conventional treatment, the addition of a tulobuterol patch may allow a more rapid positive turning point in the recovery trajectory. At the same time, PaO_2/FiO_2 on day 3 and at the end-of-treatment assessment was significantly higher in the TTS group, indicating that this adjunctive treatment was associated with a consistent direction of oxygenation improvement. As for 28-day all-cause mortality, ICU transfer, mechanical ventilation, and treatment failure, although the event rates generally favored the TTS group,

the differences did not reach statistical significance. Therefore, at the current stage these findings are more appropriately interpreted as directional signals rather than definitive evidence of prognostic benefit (*Table II*).

Comparison of dynamic changes in inflammatory markers between the two groups

Dynamic changes in inflammatory markers showed that after treatment both groups experienced declines in CRP, PCT, IL-6, and NLR, indicating that standardized treatment was effective overall; however, the declines were more marked in the TTS group than in the control group. In particular, CRP, PCT, and IL-6 showed fairly clear between-group differences both on day 3 and at the end-of-treatment assessment, suggesting that adjunctive patch therapy may be associated with a faster decline in inflammatory burden. NLR showed a statistically significant between-group difference on day 3, whereas the difference at the end-of-treatment assessment did not reach statistical significance ($P = 0.058$). This finding suggests that the between-group difference in NLR was more pronounced during the early treatment phase and gradually narrowed as the overall condition improved. It should be emphasized that this result is more appropriately understood as an accompanying biological change after optimization of the recovery trajectory, and should not be directly extrapolated to imply that TTS has an independent and specific anti-inflammatory pharmacologic effect (*Table III*).

Comparison of immune indicator changes between the two groups

In terms of immune indicators, both groups showed improvement in CD4+ T cells and NK cells after treatment compared with baseline. Among these, the increase in CD4+ T cells was more evi-

Table III Comparison of dynamic changes in inflammatory markers between the two groups.

Indicator	Time point	Control group (n=136)	TTS group (n=140)	P value
CRP (mg/L)	Baseline	97.6 +/- 28.4	100.3 +/- 30.1	0.445
	Day 3	66.2 +/- 24.7	56.4 +/- 21.8	0.001
	End-of-treatment assessment	30.5 +/- 14.2	22.8 +/- 11.7	<0.001
PCT (ng/mL)	Baseline	1.82 +/- 0.91	1.88 +/- 0.96	0.593
	Day 3	1.16 +/- 0.63	0.94 +/- 0.57	0.003
	End-of-treatment assessment	0.47 +/- 0.29	0.34 +/- 0.21	<0.001
IL-6 (pg/mL)	Baseline	63.8 +/- 22.6	65.1 +/- 24.1	0.646
	Day 3	42.6 +/- 17.5	34.7 +/- 15.4	<0.001
	End-of-treatment assessment	22.4 +/- 9.7	17.3 +/- 8.2	<0.001
NLR	Baseline	12.3 +/- 4.1	12.7 +/- 4.5	0.440
	Day 3	9.1 +/- 3.6	7.8 +/- 3.1	0.001
	End-of-treatment assessment	5.9 +/- 2.4	5.3 +/- 2.2	0.058

Table IV Comparison of immune indicator changes between the two groups.

Indicator	Time point	Control group (n=136)	TTS group (n=140)	P value
CD4+ T cells (%)	Baseline	29.1 +/- 6.2	28.7 +/- 6.5	0.596
	End-of-treatment assessment	33.2 +/- 5.8	35.8 +/- 6.0	0.001
NK cells (%)	Baseline	9.4 +/- 2.8	9.1 +/- 2.7	0.367
	End-of-treatment assessment	10.3 +/- 2.9	11.0 +/- 3.0	0.072

Note: All P values were interpreted using a two-sided significance threshold of $P < 0.05$. The end-of-treatment difference in NLR between groups was therefore considered statistically non-significant despite a numerical trend.

Table V Comparison of safety outcomes between the two groups.

Indicator	Control group (n=136)	TTS group (n=140)	P value
Total adverse reactions [n (%)]	8 (5.9)	15 (10.7)	0.140
Application-site pruritus/erythema [n (%)]	0 (0.0)	7 (5.0)	0.012
Palpitations [n (%)]	2 (1.5)	4 (2.9)	0.442
Dry mouth [n (%)]	3 (2.2)	5 (3.6)	0.496
Mild insomnia [n (%)]	1 (0.7)	3 (2.1)	0.347
Drug discontinuation [n (%)]	0 (0.0)	1 (0.7)	0.321
Serious adverse events [n (%)]	0 (0.0)	0 (0.0)	-

dent in the TTS group, and the between-group difference reached statistical significance, whereas NK cells showed only an upward trend without statistical significance. These results suggest that in elderly patients with severe pneumonia, adjunctive TTS treatment may be associated with more rapid recovery of cellular immunity; however, different immune indicators do not have the same sensitivity to treatment response, and the relevant conclusions still require further confirmation in studies with fixed time points and larger sample sizes (*Table IV*).

Comparison of safety outcomes between the two groups

In terms of safety, there was no statistically significant difference between the two groups in the overall incidence of adverse reactions, but the rate of application-site pruritus/erythema was higher in the TTS group. The between-group differences in the incidences of palpitations, dry mouth, mild insomnia, and drug discontinuation did not reach statistical significance, and no serious adverse events were observed in either group. Overall, TTS had acceptable tolerability in elderly patients with severe pneumonia, but local skin reactions should be regarded as a key safety issue requiring close observation during clinical use (*Table V*).

Discussion

This study focused on the inpatient recovery process of elderly patients with severe pneumonia who received TTS in addition to standardized conventional treatment. The results showed that compared with conventional treatment alone, the TTS group had advantages in time to clinical stability, length of hospital stay, and oxygenation improvement, suggesting that its potential benefit is more likely to be reflected first in the pace of recovery and the efficiency of supportive care rather than in obvious changes in hard clinical endpoints. For elderly patients with severe pneumonia, this finding has certain clinical significance because such patients often simultaneously face multiple problems, including infectious burden, reduced airway clearance capacity, limited baseline lung function, and insufficient systemic reserve. Treatment goals should therefore not be confined to short-term survival, but should also pay attention to the speed and quality of transition from acute imbalance to a controllable recovery stage (13, 14).

From the perspective of pharmacologic characteristics, this phenomenon is reasonably plausible. For the TTS used in this study, the specific formulation was a tulobuterol patch, which is a transdermally sustained-release beta2-receptor agonist. Previous studies and reviews have shown that this route of administration can provide relatively stable drug exposure, reduce fluctuations in drug concentration caused by frequent dosing, and lessen dependence on correct inhalation maneuvers (15–18). Therefore, in elderly, frail, low-inspiratory-force, or poorly cooperative patients, the more reasonable clinical positioning of the tulobuterol patch is adjunctive airway support rather than a substitute for the core role of anti-infective therapy.

It should be emphasized that chronic airway diseases and severe pneumonia do not belong to the same disease spectrum. Therefore, previous evidence on transdermal tulobuterol patches cannot simply be extrapolated to indicate consistent benefit for all patients with severe pneumonia. In this study, the earlier improvement in PaO_2/FiO_2 in the TTS group further suggests that TTS may create more favorable conditions for overall recovery by reducing airway resistance, improving ventilatory efficiency, and improving treatment implementation. Given that a certain proportion of patients in both groups had coexisting COPD or an underlying obstructive airway background, the advantages observed in this study may have been concentrated partly in such patients. At the current stage, therefore, TTS is more appropriately understood as an adjunctive treatment that may be of greater value in specific clinical phenotypes rather than as a universal regimen for all elderly patients with severe pneumonia.

The inflammatory marker findings should not be interpreted as evidence that TTS has a direct anti-inflammatory effect. A more appropriate explanation is that improved airway status and oxygenation may reduce overall physiological stress and support a more coordinated recovery process. Under these conditions, CRP, PCT, and IL-6 may decline more rapidly as part of the broader improvement in clinical status. Therefore, the present findings indicate that TTS was associated with more favorable inflammatory trajectories, rather than proving an independent anti-inflammatory pharmacologic effect.

The immune indicator results also need to be understood in the context of host characteristics in elderly severe pneumonia. Existing studies suggest that in elderly and frail patients with pneumonia, reduced CD4+ T cells are associated with disease severity, and some studies further indicate that CD4+ T cells combined with infection indicators may help assess disease status (19). In addition, pronounced lymphopenia or immune imbalance in patients with pneumonia often suggests more severe systemic responses and poorer short-term outcomes. In this study, the TTS group showed a greater recovery amplitude in CD4+ T cells, whereas NK cells showed only a trend toward elevation, indicating that different immune subsets do not respond with identical sensitivity to adjunctive treatment and also suggesting that the potential influence of TTS is more likely to be reflected in indirect immune benefits after improvement of the recovery environment.

In this study, although 28-day all-cause mortality, ICU transfer, mechanical ventilation, and treatment failure all favored the TTS group, none reached statistical significance, and this should be reported truthfully. In clinical studies in the field of infection, endpoints such as death and mechanical ventilation are jointly affected by multiple factors, including baseline lung function, pathogen characteristics, drug resistance, nutritional status, organ reserve, complications, and initial severity on admission. Even if TTS is truly beneficial as an adjunctive treatment, its effects are more likely to appear first in surrogate endpoints such as recovery time, oxygenation improvement, and the speed of decline in inflammatory markers, rather than quickly translate into clear differences in hard endpoints in a study with a moderate sample size. Therefore, this study does not interpret the above directional findings as definitive benefit, but only as signals worthy of further verification in larger, multicenter studies.

In terms of safety, no serious adverse events were observed in this study, providing basically acceptable evidence of tolerability for the adjunctive use of TTS in elderly patients with severe pneumonia. At the same time, the markedly increased incidence of application-site pruritus/erythema also reminds clinicians that local adverse reactions to transdermal preparations should not be overlooked. Elderly patients often have weaker skin barrier function, dry skin, or chronic skin problems; therefore, in actual use attention should be paid to rotating application sites, strengthening local skin observation, and informing patients and their families in advance about the possibility of mild discomfort. Compared with systemic adverse reactions such as palpitations and dry mouth, local skin reactions deserve greater emphasis in practical medication management.

This study still has several limitations. First, it was a single-center prospective randomized parallel-controlled study with a relatively limited sample size, and no dedicated sample-size calculation was performed for hard endpoints such as 28-day mortality, ICU transfer, or mechanical ventilation; therefore, its power to detect differences in low-event-rate outcomes remains insufficient. Second, although we attempted to standardize case screening, treatment pathways, and endpoint adjudication, the study was not blinded, and the assessment of clinical stability still contained some element of clinical judgment, so observer bias cannot be completely excluded. Third, the end-of-treatment assessment mainly used day 7 as the observation node, and for patients discharged earlier, the most recent pre-discharge result was used instead; this approach is closer to the actual hospitalization process, but it is not entirely equivalent to a strictly fixed time-point assessment, so interpretation of the final PaO_2/FiO_2 values and the final inflammatory and immune indicators still requires caution. Finally, the statistical analysis mainly centered on prespecified time points. Although overall trend evaluation was conducted for repeated measurements, multivariable adjustment and more detailed stratified analyses remained insufficient. At the same time, some patients had coexisting COPD or an obstructive airway background, and whether the benefit of TTS is concentrated more in this subgroup remains to be clarified in larger-sample, multicenter, and stratified studies.

Overall, within the framework of standardized conventional treatment, TTS may help accelerate recovery, improve oxygenation, and support more favorable inflammatory–immune changes. However, it should be regarded as an adjunctive supportive option rather than a core intervention that independently determines prognosis. This interpretation is consistent with the scope of the present study and the level of evidence currently available.

Conclusion

This study demonstrates that dynamic alterations in inflammatory and immune biomarkers are closely associated with the clinical recovery process in elderly patients with severe pneumonia. Declines

in CRP, PCT, IL-6, and NLR, together with restoration of CD4+ T-cell levels, reflect coordinated modulation of systemic inflammation and immune function. These findings support the concept that recovery from severe pneumonia is not solely a clinical process but also a biochemical transition characterized by rebalancing of inflammatory–immune homeostasis. From a translational perspective, integrated biomarker profiling may provide a valuable framework for risk stratification and real-time monitoring of therapeutic responses. Further multicenter studies incorporating predictive modeling and mechanistic exploration are warranted to validate the clinical utility of these biomarkers in precision management.

Funding

This study did not receive any funding in any form.

Conflict of interest statement

All the authors declare that they have no conflict of interest in this work.

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Received: April 15, 2026
Accepted: May 05, 2026