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SCIENTIFIC LETTER

Phenotype-based stratification and corticosteroid response in hyperinflammatory severe community-acquired pneumonia

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Dear Editor,

Severe community-acquired pneumonia (sCAP) is a frequent cause of ICU admission with a high mortality. Current international guidelines recommend systemic corticosteroids in patients with sCAP complicated by septic shock [1]. Corticosteroid indication in sCAP is probably broader, including patients with an exaggerated inflammatory response [2]. However, treatment effects remain heterogeneous, and it is increasingly recognized that the degree of systemic inflammation rather than pneumonia severity alone may be a key determinant of response [3]. Whether distinct clinical and biological phenotypes within an inflamed severe pneumonia population influence outcomes or modify corticosteroid effectiveness remains uncertain.

We explored phenotype heterogeneity in a cohort of patients with sCAP and high inflammatory response (C-reactive protein > 150 mg/L at admission) enrolled in a randomized trial where patients received either intravenous methylprednisolone (0.5 mg/kg every 12 h for 5 days) or placebo, initiated within 36 h of hospital admission [4]. Our objectives were to identify data-driven phenotypes using baseline clinical and biological variables and to evaluate whether phenotype was associated with clinical outcomes or modified the effect of adjunctive corticosteroid therapy.

All analyses were conducted in the intention-to-treat population. Continuous variables are reported as mean (standard deviation) or median (interquartile range), and categorical variables as counts and percentages. Comparisons were performed using Student's *t* test or Mann Whitney *U* test for continuous variables and chi-square or Fisher's exact test for categorical variables. Multiple imputation by fully conditional specification was applied to generate five imputed datasets, incorporating demographic, comorbidity, physiological, and laboratory variables; outcomes were not imputed. The local ethics committees approved the study protocol and written informed consent was obtained from all participants or their authorized representatives.

Phenotypes were identified using a two-step cluster analysis performed on the imputed baseline dataset. Continuous variables were standardized and categorical variables entered as nominal. The optimal number of clusters was determined by the Bayesian Information Criterion (Supplementary Figure S1), and cluster quality was assessed using the silhouette coefficient (Supplementary Figure S2). Treatment allocation and outcomes were excluded from clustering. After phenotype assignment, treatment allocation and clinical outcomes (treatment failure, early and late treatment failure, and in-hospital mortality) were compared across phenotypes using chi-square or Fisher's exact tests and logistic regression models. Both unadjusted and adjusted models were fitted, with adjusted models including the Pneumonia Severity Index (PSI), the year of admission, and the center as covariates. Interaction terms between phenotype and treatment were included to assess effect modification. In

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Table 1 Baseline characteristics, treatment allocation, and outcomes by phenotype

Variable	Phenotype 1 (n = 47)	Phenotype 2 (n = 73)	P-Values
Age, years, median (IQR)	50 (32; 60)	80 (69; 82)	< 0.001
Female sex, n (%)	29 (61.7)	17 (23.3)	< 0.001
Comorbidities, n (%)[a]			
Diabetes mellitus	1 (2.1)	22 (30.1)	< 0.001
Hypertension	3 (6.4)	43 (58.9)	< 0.001
Ischemic heart disease	0 (0)	21 (28.8)	< 0.001
Chronic obstructive pulmonary disease	0 (0)	19 (26)	< 0.001
Obesity	0 (0)	9 (12.3)	< 0.012
Active cancer	1 (2.1)	10 (13.7)	0.049
Current smoker	20 (42.6)	12 (16.4)	< 0.001
Alcoholism	0 (0)	10 (13.7)	0.006
Symptoms, n (%)			
Fever	38 (80.9)	51 (69.9)	0.180
Altered mental status	0 (0)	27 (37.0)	< 0.001
Breathlessness	26 (55.3)	45 (61.6)	0.491
Cough	36 (76.6)	50 (68.5)	0.336
Chills	23 (48.9)	20 (27.4)	0.016
Chest pain	25 (53.2)	22 (30.1)	0.012
Clinical signs, median (IQR)			
Temperature, ºC	37.9 (36.8; 38.9)	37.3 (36.5; 38.2)	0.142
Respiratory rate, breaths per minute	30 (25 to 40)	27 (21.3 to 32)	0.013
Heart rate, beats per minute	115 (97.5; 129)	100 (90; 119)	0.003
Serum levels, median (IQR)			
Glucose, mg per decilitre	110 (93; 137)	149 (116; 198)	< 0.001
Platelets, $\times 10^9$ per litre	194 (155; 283)	222 (181; 286)	0.144
White blood cell count, $\times 10^9$ per litre	11.7 (7.13; 16.1)	14.9 (10.3; 22.9)	0.004
C-reactive protein, mg per litre	276 (214; 347)	278 (197; 320)	0.437
Creatinine, mg per decilitre	1.20 (0.90; 1.60)	1.60 (1.00; 1.90)	0.018
Procalcitonin, ng per mililitre	1.71 (0.50; 5.57)	1.84 (0.50; 7.33)	0.393
IL-6, pg per mililitre	399 (213; 978)	212 (134; 453)	0.002
IL-8, pg per mililitre	93 (52.5; 321)	62.5 (36; 114.5)	0.052
IL-10, pg per mililitre	7.6 (4.2; 15.5)	4.9 (2.8; 9.35)	0.041
PaO_2/FiO_2 ratio, mmHg, median (IQR)	231 (162; 281)	238 (195; 270)	0.519
Pleural effusion, n (%)	11 (23.4)	12 (16.4)	0.344
PSI score, median (IQR)	90 (53; 110)	130 (100; 140)	< 0.001
Risk class, n (%)[b]			< 0.001
I-III	23 (48.9)	9 (12.4)	
IV	20 (42.6)	27 (37.0)	
V	4 (8.5)	37 (50.7)	
Major severity criteria, n (%)			
Mechanical ventilation	4 (8.5)	11 (15.3)	0.277
Septic shock	17 (36.2)	11 (15.3)	0.009
Minor severity criteria, n (%)			
Systolic blood pressure < 90 mmHg	13 (27.7)	15 (20.8)	0.391
Multilobar involvement	31 (66.0)	40 (54.8)	0.225
PaO_2/FiO_2 ratio < 250 mmHg	31 (66.0)	51 (70.8)	0.574
ICU admission, n (%)	41 (87.2)	47 (64.4)	0.006
Macrolide combination therapy, n (%)	5 (10.6)	23 (32.4)	< 0.001

Table 1 (continued)

Variable	Phenotype 1 (n = 47)	Phenotype 2 (n = 73)	P-Values
Time from emergency department presentation to randomization, days, median (IQR)	0 (0; 1)	1 (0; 1)	0.098
Methylprednisolone treatment, n (%)	25 (53.2)	36 (49.3)	0.678
Treatment failure, n (%)	10 (21.3)	16 (21.9)	0.934
Early treatment failure (0-72 h)	6 (12.8)	6 (8.2)	0.536
Early mechanical ventilation	6 (12.8)	3 (4.1)	0.152
Early septic shock	0 (0)	5 (6.8)	0.155
Death	1 (2.1)	3 (4.1)	> 0.999
Late treatment failure (72-120 h)	6 (12.8)	11 (15.1)	0.724
Radiographic progression	3 (6.4)	7 (9.6)	0.738
Respiratory failure	1 (2.1)	5 (6.8)	0.402
Late mechanical ventilation	1 (2.1)	4 (5.5)	0.647
Late septic shock	2 (4.3)	2 (2.7)	0.644
Death	0 (0%)	0 (0%)	–
In-hospital mortality, n (%)	2 (4.3)	13 (17.8)	0.028

IQR interquartile range; *PSI* Pneumonia Severity Index

[a] Could have more than 1 comorbid condition

[b] Stratified according to 30-day risk mortality for community-acquired pneumonia: risk classes I-III (90 points) have low mortality (range, 0%-10%) and risk class IV (91–130 points) and risk class V (> 130 points) have the highest mortality (range, 10%-35%)

addition to the overall population, prespecified subgroup analyses were performed according to baseline C-reactive protein concentration, using a cutoff value of 204 mg/L as described [5]. Analyses were performed using SPSS Statistics version 26.

A total of 120 patients were included (59 placebo, 61 methylprednisolone). Baseline characteristics were well balanced between treatment groups. All patients exhibited a marked inflammatory response at presentation, with median C-reactive protein values exceeding 200 mg/L, consistent with the enrichment strategy of the parent trial.

Two distinct phenotypes were identified (Supplementary Table S1). Phenotype one accounted for 39% of patients and was characterized by younger age, a predominance of women, and a very low burden of chronic comorbidities. Patients in this phenotype presented with higher respiratory and heart rates, frequent fever and preserved metabolic and renal function. Phenotype two accounted for 61% of patients and was characterized by older age, male predominance, and a high prevalence of chronic comorbidities (diabetes, hypertension, COPD, and ischemic heart disease). Altered mental status was common, and laboratory findings showed higher leukocyte and neutrophil counts with worse metabolic and renal profiles. Despite these differences, baseline C-reactive protein concentrations and oxygenation indices were similar between phenotypes. Treatment allocation did not differ between phenotypes, indicating that phenotype assignment was independent of randomization.

Overall, treatment failure occurred in 22% of patients and did not differ between phenotypes (phenotype one: 10/47 [21%] vs. phenotype two: 16/73 [22%]; p = 0.934). In adjusted logistic regression, phenotype membership was not associated with treatment failure (aOR 0.61, 95% CI 0.21 to 1.78; p = 0.366, Supplementary Table S2). Within both phenotypes, treatment failure occurred less frequently among patients treated with methylprednisolone compared with placebo (phenotype one: 4/25 [16%] vs. 6/22 [27%]; phenotype two: 4/36 [11%] vs. 12/37 [32%]). However, there was no evidence of effect modification (phenotype-by-treatment interaction; Supplementary Table S3). Findings were consistent for early and late treatment failure, and in analyses restricted to patients with baseline CRP ≥ 204 mg/L [5] (Supplementary Tables S4-S5).

In-hospital mortality was higher in phenotype two than in phenotype one (13/73 [18%] vs. 2/47 [4%]; p = 0.028). After adjustment, phenotype was not independently associated with in-hospital mortality (aOR 1.43, 95% CI 0.25 to 8.22; p = 0.686; Supplementary Table S2). Mortality was numerically lower with methylprednisolone than with placebo in phenotype two, whereas little difference was observed in phenotype one (phenotype one: 1/25 [4%] vs. 1/22 [5%]; phenotype two: 5/36 [14%] vs. 8/37 [22%]); however, no statistically significant

phenotype-by-treatment interaction was detected (Supplementary Table S3). Results were similar in analyses restricted to patients with baseline CRP ≥ 204 mg/L [5] (Table 1).

In patients with sCAP and high inflammatory response, two clinically and biologically distinct phenotypes were identified using an unsupervised, data-driven approach. Despite marked differences in age, comorbidity burden, physiological presentation, and laboratory profiles, phenotype was not associated with clinical outcomes and did not modify the effect of adjunctive methylprednisolone. These findings suggest that, in a population selected for high inflammatory response, corticosteroid efficacy may be largely independent of broader clinical phenotype and support treatment decisions based on overall disease severity and inflammatory burden rather than phenotype stratification alone as we recently suggested [5]. However, given the substantially higher overall mortality observed in phenotype two (18%), future RCTs could focus enrolment on this higher risk phenotype, while maintaining systemic inflammation enrichment (at least 150 mg/L [2]). Such an approach may increase event rates, statistical power, and feasibility in future interventional studies for severe pneumonia.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1007/s00134-026-08373-x.

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Data availability
The database can be made available upon request to the corresponding author.

Declarations

Conflicts of interest
The authors declare no conflicts of interest or funding.

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