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Association of Hyperinflammatory and Hypoinflammatory Sepsis Phenotypes with ICU Mortality and Length of Stay: A Prospective Cohort Study

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ABSTRACT: Sepsis is biologically heterogeneous, and inflammatory phenotypes may provide clinically relevant prognostic information in addition to conventional severity assessment, although their incremental prognostic value requires further evaluation. This study evaluated the association of hyperinflammatory and hypoinflammatory sepsis phenotypes with ICU mortality and length of stay. This prospective cohort study included adults with sepsis admitted to the ICU of Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia, from July to September 2026. Phenotypes were assigned by a prespecified algorithm using laboratory and clinical parameters within 24 hours of diagnosis. Analyses compared hyperinflammatory and hypoinflammatory patients; intermediate or unclassified phenotypes were described separately. ICU mortality, length of stay, and classification stability were assessed. Among 108 patients, 45 (41.7%) were hyperinflammatory, 52 (48.1%) hypoinflammatory, and 11 (10.2%) intermediate or unclassified. Analysis included 97 patients. ICU mortality was higher in the hyperinflammatory than hypoinflammatory group (31.1% vs 13.5%; unadjusted risk ratio, 2.31 [95% CI, 1.02–5.22]; $p = 0.035$), and ICU stay was longer (median, 12 vs 10 days; $p = 0.009$). Bootstrap showed phenotype proportions, and sensitivity showed substantial-to-almost-perfect agreement after sequential exclusion. In this single-centre cohort, hyperinflammatory sepsis was associated with higher observed ICU mortality and longer ICU length of stay than hypoinflammatory sepsis. Independent external validation and assessment of incremental prognostic value beyond established severity scores are required before clinical implementation.

1. INTRODUCTION

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, and remains a major challenge in intensive care medicine [1–3]. Globally, sepsis accounted for an estimated 48.9 million cases and 11 million deaths in 2017, underscoring its substantial contribution to preventable mortality [4,5]. Among critically ill patients, the epidemiology and outcomes of sepsis vary across regions and health-care settings, reflecting differences in case mix, resources, and ICU practice [6,7].

This variability indicates that sepsis is biologically heterogeneous, as patients with apparently similar clinical severity may exhibit distinct immune responses, trajectories of organ dysfunction, and outcomes [8–10]. Hyperinflammatory and hypoinflammatory

subphenotypes have been identified in sepsis and are associated with different inflammatory profiles and mortality risks ^[11]. A hyperinflammatory phenotype can be identified through combined clinical and biomarker data and has been associated with a higher risk of death than less inflammatory phenotypes ^[12]. However, clinically feasible and externally validated approaches for identifying ICU subphenotypes remain a priority for precision medicine in critical care ^[13].

Inflammatory biomarkers, including interleukin-6, may support early risk stratification because elevated concentrations are associated with greater disease severity and poorer outcomes in sepsis ^[14]. Procalcitonin, C-reactive protein, neutrophil-to-lymphocyte ratio, hematological indices, and physiological parameters may complement clinical assessment by characterising systemic inflammatory activity ^[15,16]. Therefore, this prospective cohort study evaluated the association of hyperinflammatory and hypoinflammatory sepsis phenotypes, classified using laboratory and clinical parameters within 24 hours of diagnosis, with ICU mortality and ICU length of stay in an Indonesian tertiary-care setting.

2. MATERIALS AND METHODS

2.1 Study Design and Setting

This prospective observational cohort study was conducted in the ICU of Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia, from July to September 2026. Consecutive eligible patients were enrolled at the time of sepsis diagnosis and followed until ICU discharge or death. The target sample size was 105 patients, calculated for comparison of two mortality proportions with unequal group allocation, 80% power, a two-sided alpha of 0.05, and an anticipated 15% attrition rate.

2.2 Participants

Adults aged 18 years or older with sepsis, defined according to Sepsis-3 criteria, were eligible for inclusion [1]. Participants were required to have complete measurements of IL-6, PCT, CRP, NLR, bicarbonate, body temperature, leukocyte count, platelet count, MAP, and lactate within 24 hours of sepsis diagnosis, as well as complete ICU outcome data. Patients were excluded if they declined consent, had incomplete baseline biomarker or clinical data, had a severe haematological disorder, had severe immunosuppression, or were transferred from another ICU without adequate baseline data. Patients with haemolysed blood specimens, withdrawal of consent, or incomplete follow-up data were excluded from the final analysis. For this study, Sepsis-3 required suspected or confirmed infection together with an acute increase in SOFA score of at least 2 points from baseline.

2.3 Data Collection and Phenotype Classification

Demographic characteristics, comorbidities, clinical data, laboratory findings, and treatment-related variables were recorded prospectively using standardised case-report forms. IL-6 was measured by immunoassay, PCT by chemiluminescent immunoassay, CRP by turbidimetry, and bicarbonate by arterial blood gas analysis; NLR was calculated from the complete blood count. Temperature, leukocyte count, platelet count, MAP, lactate, and early haemodynamic response were obtained from ICU monitoring and medical records. The 24-hour measurement window began at the documented time of sepsis diagnosis; the baseline laboratory and clinical values recorded within that prespecified window were used for phenotype classification.

A prespecified rule-based classification algorithm was applied using data obtained within 24 hours of diagnosis. The corresponding thresholds were selected a priori from reported associations between inflammatory biomarkers, hematological abnormalities, metabolic derangement, and adverse outcomes in sepsis, together with clinically established reference ranges; outcome data from the present cohort were not used to derive or optimise these thresholds. Hyperinflammatory phenotype was assigned when at least four hyperinflammatory criteria were present: IL-6 ≥ 300 pg/mL, PCT ≥ 2 ng/mL, CRP ≥ 150 mg/L, NLR ≥ 10 , bicarbonate < 20 mmol/L, temperature $\geq 38.5^\circ\text{C}$, leukocyte count $\geq 12,000/\mu\text{L}$, platelet count $\geq 150,000/\mu\text{L}$, and rapid haemodynamic stabilisation. Hypoinflammatory phenotype was assigned when at least four hypoinflammatory criteria were present: IL-6 < 100 pg/mL, PCT < 0.5 ng/mL, CRP < 50 mg/L, NLR < 3 , bicarbonate > 22 mmol/L, temperature $< 36^\circ\text{C}$, leukocyte count $\leq 4,000/\mu\text{L}$, platelet count $< 100,000/\mu\text{L}$, and delayed or unstable haemodynamic response. Patients meeting fewer than four criteria for either phenotype were categorised as unclassified/intermediate and were reported descriptively but excluded from the prespecified primary comparative analysis. The same prespecified rules were applied before outcome comparisons, and the intermediate/unclassified category was retained as a distinct descriptive category rather than reassigned to either comparison group.

Haemodynamic response was assessed during the first 6 h after initiation of resuscitation. Rapid haemodynamic stabilisation was defined as achievement and maintenance of MAP ≥ 65 mmHg within 6 h without subsequent escalation of vasopressor support. Delayed or unstable haemodynamic response was defined as persistent hypotension, failure to achieve or maintain MAP ≥ 65 mmHg within 6 h, and/or continued escalation of vasopressor support beyond this period.

2.4 Outcomes and Covariates

The primary outcome was ICU mortality, defined as death from any cause during ICU admission. The secondary outcome was ICU length of stay, calculated from ICU admission to ICU discharge or death. Prespecified covariates included age, sex, comorbidities, baseline SOFA score, immune status, and receipt of early treatment, including antibiotics or vasopressors before ICU admission. Length of stay was treated as an observed ICU outcome rather than an independent recovery measure because death during ICU admission can truncate the duration of stay.

2.5 Internal Stability Assessment of Phenotype Classification

Internal stability of the classification algorithm was assessed using 1,000 bootstrap resamples. The phenotype algorithm was reapplied in each resample, and the stability of phenotype proportions was evaluated using bootstrap-derived 95% CIs. Agreement between classifications in the original and resampled datasets was assessed using Cohen's kappa where applicable. A leave-one-parameter-out sensitivity analysis was also performed to evaluate the influence of individual classification parameters on phenotype assignment. These analyses assessed internal classification stability and did not constitute external validation.

2.6 Statistical Analysis

Continuous data were assessed for distribution using the Shapiro–Wilk test, histograms, and Q–Q plots. Normally distributed variables were reported as mean $\pm$ standard deviation and compared using the independent-samples t-test, whereas non-normally distributed variables were reported as median [range] and compared using the Mann–Whitney U test. Categorical variables were presented as frequency (%) and compared using the chi-square or Fisher's exact test, as appropriate. All tests were two-sided, and p values < 0.05 were considered statistically significant. ICU mortality was compared without covariate adjustment; the reported risk ratio and 95% CI are therefore unadjusted associations. Given the limited number of ICU deaths, no multivariable mortality model was fitted to avoid unstable estimates. ICU length of stay was analysed from ICU admission to discharge or death and interpreted cautiously in view of death as a competing event.

2.7 Missing Data and Analytical Scope

Eligibility required complete measurements for all phenotype variables and complete ICU outcome data. The comparative analysis was therefore a complete-case analysis, and no imputation was performed. Aggregate screening and pre-inclusion exclusion counts were not retained in the available study records; consequently, a full screening flow before the 108 included participants could not be reconstructed.

3. RESULTS AND DISCUSSION

3.1 Study Population and Baseline Characteristics

A total of 108 patients with sepsis were included in the study. Of these, 45 patients (41.7%) were classified as hyperinflammatory, 52 (48.1%) as hypoinflammatory, and 11 (10.2%) as intermediate/unclassified. The prespecified primary comparative analysis therefore included 97 patients with either hyperinflammatory or hypoinflammatory phenotype (Figure 1); the intermediate/unclassified group was reported descriptively. No statistically significant differences were observed in the measured baseline demographic characteristics, comorbidities, or illness-severity scores between the two phenotype groups (Table 1). The median age was 55 years in the hyperinflammatory group and 60 years in the hypoinflammatory group ($p = 0.134$), while male participants accounted for 55.6% and 67.3% of the groups, respectively ($p = 0.235$). The prevalence of hypertension, type 2 diabetes mellitus, coronary artery disease, chronic kidney disease, and chronic liver disease did not differ significantly. Likewise, median GCS, SOFA, and APACHE II scores did not differ significantly between phenotypes. Nevertheless, residual baseline imbalance cannot be excluded given the modest sample size.

3.2 Phenotype Characteristics

As expected from the prespecified classification criteria, the two phenotype groups exhibited distinct distributions of the biomarker, haematological, metabolic, and haemodynamic variables used in the classification algorithm (Supplementary Table S1). These differences are presented descriptively because the variables contributed directly to phenotype assignment. Haemodynamic stability was more frequent in the hyperinflammatory group than in the hypoinflammatory group (73.3% vs 26.9%, $p < 0.001$). Conversely, haemodynamic instability was observed in 73.1% of patients with the hypoinflammatory phenotype.

Table 1. Baseline characteristics of patients with hyperinflammatory and hypoinflammatory sepsis

Characteristic	Hyperinflammatory (n = 45)	Hypoinflammatory (n = 52)	p value
Age, years	55 [21–77]	60 [24–75]	0.134
Male sex	25 (55.6)	35 (67.3)	0.235
Hypertension	14 (31.1)	14 (26.9)	0.650
Type 2 diabetes mellitus	23 (51.1)	22 (42.3)	0.386
Coronary artery disease	5 (11.1)	4 (7.7)	0.563
Chronic kidney disease	13 (28.9)	23 (44.2)	0.119
Chronic liver disease	1 (2.2)	2 (3.8)	0.641
GCS score	14 [11–15]	14 [7–15]	0.232
SOFA score	7 [3–11]	7 [2–14]	0.559
APACHE II score	22 [11–31]	22 [11–32]	0.674

Data are presented as median [range] or n (%). Continuous variables were compared using the Mann–Whitney U test and categorical variables using the chi-square test.

3.3 ICU Mortality and Length of Stay

ICU mortality differed significantly between phenotypes (Table 2). Fourteen of 45 patients with hyper-inflammatory sepsis died in the ICU (31.1%), compared with 7 of 52 patients with hypoinflammatory sepsis (13.5%; unadjusted risk ratio, 2.31 [95% CI, 1.02–5.22]; $p = 0.035$). The median ICU length of stay was also longer in the hyperinflammatory group than in the hypoinflammatory group, at 12 days (range, 4–16) versus 10 days (range, 2–14), respectively ($p = 0.009$; Table 2). Because ICU death may truncate length of stay, this finding should be interpreted cautiously. These between-phenotype estimates are unadjusted and should not be interpreted as evidence of an independent causal effect of phenotype.

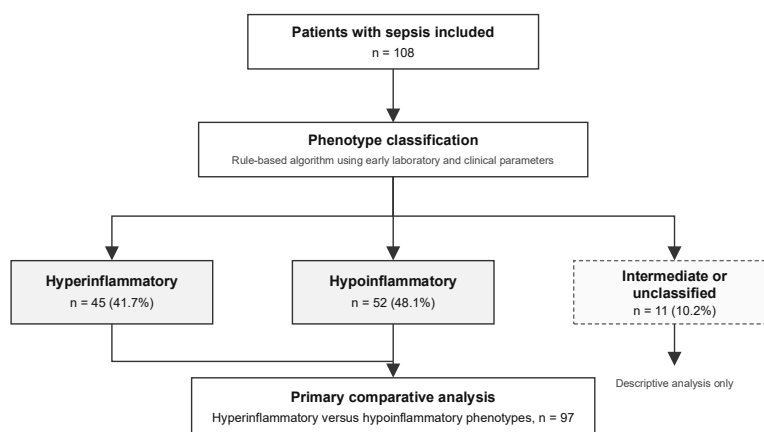


Figure 1. Patient flow and sepsis phenotype classification. Intermediate or unclassified patients were included in the descriptive analysis but excluded from the primary comparative analysis.

Table 2. ICU outcomes according to sepsis phenotype

Outcome	Hyperinflammatory (n = 45)	Hypoinflammatory (n = 52)	<i>p</i> value
ICU mortality	14 (31.1)	7 (13.5)	0.035
ICU length of stay, days	12 [4–16]	10 [2–14]	0.009
Unadjusted risk ratio for ICU mortality	2.31	95% CI, 1.02–5.22	

Data are presented as n (%) or median [range]. ICU mortality was compared using the chi-square test and is additionally reported with an unadjusted risk ratio and 95% CI; ICU length of stay was compared using the Mann–Whitney U test.

3.4 Internal Stability Assessment of the Phenotype Classification

Bootstrap resampling demonstrated stable phenotype proportions across 1,000 resamples (Table 3). The observed proportions of hyperinflammatory and hypoinflammatory phenotypes were 46.4% and 53.6%, respectively, and both values fell within their corresponding bootstrap 95% CIs. In leave-one-parameter-out sensitivity analyses, phenotype reassignment ranged from 2.8% to 17.6% and Cohen’s kappa values ranged from 0.725 to 0.953 (Supplementary Table S2). Excluding PCT, bicarbonate, body temperature, or haemodynamic response produced the greatest change in classification (17.6% each; $\kappa = 0.725$), whereas excluding NLR produced the smallest change (2.8%; $\kappa = 0.953$). These analyses assess internal classification stability rather than external validity.

Table 3. Bootstrap assessment of phenotype classification stability among the comparative cohort

Phenotype	Patients, <i>n</i>	Observed proportion, %	Bootstrap 95% CI	Bias	Standard error	Interpretation
Hyperinflammatory	45	46.4	37.1–56.7	–0.1	5.0	Stable
Hypoinflammatory	52	53.6	43.3–62.9	+0.1	5.0	Stable

Bootstrap assessment of phenotype classification stability was performed using 1,000 resamples with replacement. The analysis included 97 patients classified as hyperinflammatory or hypoinflammatory; intermediate or unclassified patients were excluded from the comparative cohort.

3.5 Discussion

The present study identified hyperinflammatory and hypoinflammatory sepsis phenotypes within a prospective ICU cohort. No statistically significant differences were observed in measured demographic characteristics, comorbidity profiles, or baseline severity scores between the groups; however, the modest sample size means that residual baseline imbalance cannot be excluded. The observed outcome differences were associated with phenotype classification, but causal interpretation is not warranted because residual and unmeasured confounding remain possible. These findings are in line with Sinha et al. (2023)^[11], who identified reproducible inflammatory subphenotypes across prospective sepsis cohorts despite differences in patient populations and clinical settings.

The phenotype groups had divergent distributions of inflammatory, haematological, metabolic, and haemodynamic variables. Because these variables formed part of the prespecified classification algorithm, these differences should be interpreted descriptively rather than as independent validation of the phenotype. The multidimensional profile is consistent with reports that sepsis subphenotypes reflect coordinated biological states rather than isolated abnormalities in a single biomarker. Similarly, Halstead et al. (2025) demonstrated that inflammatory subphenotypes of critical illness can be distinguished using combined immune and biochemical measurements^[17].

Hyperinflammatory sepsis was associated with higher ICU mortality than hypoinflammatory sepsis. This finding is in line with Sinha et al. (2023)^[11], who reported consistently greater mortality among hyperinflammatory patients across two prospective sepsis cohorts. It is also consistent with the latent-class analysis by DeMerle et al. (2024)^[12], in which the hyperinflammatory phenotype was associated with a substantially higher risk of death. Potential biological mechanisms include excessive

inflammatory activation, endothelial injury, microcirculatory dysfunction, and progressive organ failure; however, these mechanisms cannot be inferred from the present observational data. The observed association supports further evaluation of early phenotypic stratification, rather than establishing a causal effect.

The hyperinflammatory phenotype was also associated with a longer ICU length of stay. This pattern agrees with findings by Halstead et al. (2025)^[17], in which persistent hyperinflammatory characteristics were associated with less favourable clinical trajectories. However, ICU death may truncate length of stay; therefore, the observed difference should be interpreted cautiously. Future analyses that account for death as a competing event or assess ICU length of stay among survivors would help clarify this association.

The bootstrap and leave-one-parameter-out analyses indicated that the rule-based classification was internally stable across resampled datasets and retained moderate-to-high robustness when individual parameters were sequentially removed. The strongest influence on classification was observed for PCT, bicarbonate, body temperature, and haemodynamic response, whereas no single parameter wholly determined phenotype assignment. Because haemodynamic response may be influenced by resuscitation and vasopressor management, its contribution should be examined further in analyses that omit this component. These findings support the need for independent validation of a combined biomarker–clinical classification approach.

This study has several limitations. First, the single-centre design and modest sample size may limit statistical precision, particularly for analyses of mortality, and may reduce the generalisability of the findings to ICUs with different patient characteristics, infection epidemiology, and treatment practices. Second, phenotype assignment was based on a prespecified rule-based algorithm using biomarker and clinical thresholds rather than latent class analysis or unsupervised clustering. No universally accepted criteria currently define hyperinflammatory and hypoinflammatory sepsis phenotypes, and the algorithm requires external validation in independent cohorts. Furthermore, the rule-based phenotype definition was evaluated within the same cohort in which the clinical associations were examined; therefore, the findings should be considered hypothesis-generating until replicated in an independent population.

Third, residual confounding from unmeasured factors, including pathogen characteristics, genetic susceptibility, nutritional status, immunomodulatory treatment, and variations in early sepsis management, cannot be excluded. Biomarker measurements were obtained through routine laboratory methods and may be subject to analytical variability; moreover, the availability of IL-6 may limit the immediate applicability of this classification approach in resource-constrained settings. The inclusion of haemodynamic response as one component of phenotype classification may introduce treatment-related variability because haemodynamic trajectories are influenced by fluid resuscitation and vasopressor management. Finally, the study assessed ICU mortality and ICU length of stay only and did not evaluate longer-term outcomes, including post-ICU mortality, persistent organ dysfunction, functional status, or quality of life, which are important components of sepsis survivorship. In addition, the absence of aggregate screening and pre-inclusion exclusion counts precluded reconstruction of a complete recruitment flow. The timing of individual measurements within the 24-hour window and the influence of early resuscitation or vasopressor treatment were not analysed separately. Mortality estimates were unadjusted because of the limited number of deaths, and ICU length of stay was measured to discharge or death; thus, residual confounding and death as a competing event limit interpretation of the observed associations.

4. CONCLUSION

In this prospective single-centre ICU cohort, a prespecified rule-based inflammatory phenotype was associated with ICU mortality and ICU length of stay. Patients classified as hyperinflammatory had a higher observed ICU mortality and longer ICU stay than those classified as hypoinflammatory. The classification showed internal stability within this cohort; however, independent external validation and assessment of its incremental prognostic value beyond established severity scores are required before clinical implementation.

AUTHOR CONTRIBUTIONS

CWS: Conceptualization, Methodology, Investigation, Data Curation, Formal Analysis, Visualization, Writing – Original Draft. SHS: Conceptualization, Methodology, Supervision, Writing – Review and Editing. FM: Methodology, Supervision, Writing – Review and Editing. H: Methodology, Supervision, Writing – Review and Editing. MR: Methodology, Supervision, Writing –

Review and Editing. ASP: Methodology, Supervision, Writing – Review and Editing. HN: Validation, Writing – Review and Editing. All authors read and approved the final manuscript.

CONFLICT OF INTEREST

The authors declare that they have no competing interests.

ETHICS STATEMENT

The study protocol was approved by the Ethics Committee of the Faculty of Medicine, Hasanuddin University, RSPTN Hasanuddin University, and Dr. Wahidin Sudirohusodo Hospital, Makassar, Indonesia (approval No. 782/UN4.6.4.5.31/PP36/2026; 23 June 2026). Written informed consent was obtained from all participants or their legally authorised representatives before enrolment.

DATA AVAILABILITY STATEMENT

The datasets generated and analysed during the current study are available from the corresponding author upon reasonable request, subject to institutional and ethical requirements.

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Supplementary Table S1. Biomarker, clinical, and haemodynamic characteristics according to sepsis phenotype

Variable	Hyperinflammatory (n = 45)	Hypoinflammatory (n = 52)	p value
IL-6, pg/mL	363.80 [136.10–1800.00]	65.10 [7.70–299.40]	<0.001
PCT, ng/mL	2.78 [0.87–11.73]	0.48 [0.06–1.95]	<0.001
hs-CRP, mg/L	211.50 [66.10–450.00]	47.70 [13.40–343.90]	<0.001
NLR	6.76 [3.75–29.03]	2.98 [1.66–7.18]	<0.001
Bicarbonate, mmol/L	18.60 [13.10–24.70]	24.35 [18.00–30.00]	<0.001
Body temperature, °C	38.50 [36.90–39.50]	35.70 [34.30–37.10]	<0.001
Leukocyte count, $\times 10^3/\mu\text{L}$	12.74 [4.06–27.22]	4.39 [1.37–13.67]	<0.001
Platelet count, $\times 10^3/\mu\text{L}$	156.0 [61.0–296.0]	84.0 [25.0–172.0]	<0.001
Haemodynamically stable	33 (73.3)	14 (26.9)	<0.001
Haemodynamically unstable	12 (26.7)	38 (73.1)	<0.001

Data are presented as median [range] or n (%). Variables shown in this table contributed directly to phenotype assignment; comparisons are therefore descriptive and should not be interpreted as independent validation of the phenotype classification.

Supplementary Table S2. Leave-one-parameter-out sensitivity analysis of phenotype classification

Parameter excluded from algorithm	Patients, n	Reclassified patients, n (%)	Cohen's κ	Interpretation
IL-6	97	13 (12.04)	0.807	Almost perfect agreement
PCT	97	19 (17.59)	0.725	Substantial agreement
hs-CRP	97	16 (14.81)	0.733	Substantial agreement
NLR	97	3 (2.78)	0.953	Almost perfect agreement
Bicarbonate	97	19 (17.59)	0.725	Substantial agreement
Body temperature	97	19 (17.59)	0.725	Substantial agreement
Leukocyte count	97	11 (10.19)	0.834	Almost perfect agreement
Platelet count	97	7 (6.48)	0.893	Almost perfect agreement
Haemodynamic response	97	19 (17.59)	0.725	Substantial agreement

The reference classification used all nine parameters. Agreement was interpreted using the Landis and Koch criteria: 0.61–0.80, substantial agreement; 0.81–1.00, almost perfect agreement.