Critical Care

CORRESPONDENCE

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Lymphocyte count trajectories are associated with the prognosis of sepsis patients

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Sepsis causes multiorgan dysfunction from immune dysregulation, resulting in high ICU admissions and mortality [1]. Lymphocytes are essential in the immune response during sepsis, with lymphopenia linked to increased vulnerability to secondary infections, higher sepsis severity, and mortality [2]. However, prior studies primarily analyzed lymphocyte counts at fixed time points, overlooking their dynamic nature and association with sepsis prognosis. Furthermore, unlike other complex immune biomarkers such as HLA-DR, lymphocyte count is easily accessible, making it a valuable marker for continuous monitoring of immune status. This study aims to identify heterogeneous lymphocyte count trajectories in sepsis patients by leveraging the group-based trajectory modeling (GBTM) [3], which accommodates unbalanced panels and missing values.

This is a retrospective study based on data from the Medical Information Mart for Intensive Care IV (MIMIC-IV) v3.1 database (certification number: 64590357). We extracted data on 24,792 adult sepsis patients admitted to the ICU, diagnosed using Sepsis-3.0 criteria (suspected infection and a SOFA score increase of ≥ 2). After excluding patients with conditions such as long-term steroid use, transplant status, malignancy, rheumatic disease, or hematologic disease (detailed information provided in Table S1), 12,078 cases were retained. Among these, 3152 sepsis patients who had at least two lymphocyte count measurements within 7 days of ICU admission were included, with a hospital mortality rate of 24.6%.

We applied GBTM to identify lymphocyte count trajectories, selecting a three-class model (Fig. 1), based on the Akaike and Bayesian information criterion, and clinical rationality (Table S2). Trajectory 1, the "Rapid-slow decrease" class, included 525 (16.7%) patients and was characterized by a rapid decrease in lymphocyte counts in the first 3 days, followed by a slower decline. Trajectory 2, the "Stable" class, included 1453 (46.1%) patients with relatively stable lymphocyte counts. Trajectory 3, the "Rapid-slow increase" class, included 1174 (37.2%) patients who showed a rapid increase in lymphocyte counts in the first 3 days, followed by a slower rise at relatively low levels. Baseline characteristics varied significantly across these trajectories (Table 1). Patients in Trajectory 3 had the longest hospital stays, higher APSIII, OASIS, and MELD scores, and a greater prevalence of comorbidities, with the highest 28-day mortality (22.9%). In contrast, patients in Trajectory 1 had the shortest hospital stays but higher SIRS score and the highest 7-day mortality (12%).

Cox regression analysis and Kaplan–Meier survival curves were used to examine the relationship between lymphocyte trajectories and mortality. Compared to Trajectory 2, Trajectory 3 was associated with increased 28-day mortality (HR 1.61, 95% CI 1.34–1.92, $p < 0.001$), while Trajectory 1 was linked to higher 7-day mortality (HR 1.58, 95% CI 1.16–2.15, $p = 0.004$). After adjusting for confounders, Trajectory 3 remained an independent risk factor of both 7-day and 28-day mortality, while Trajectory 1 was no longer significant (Table 2). Survival

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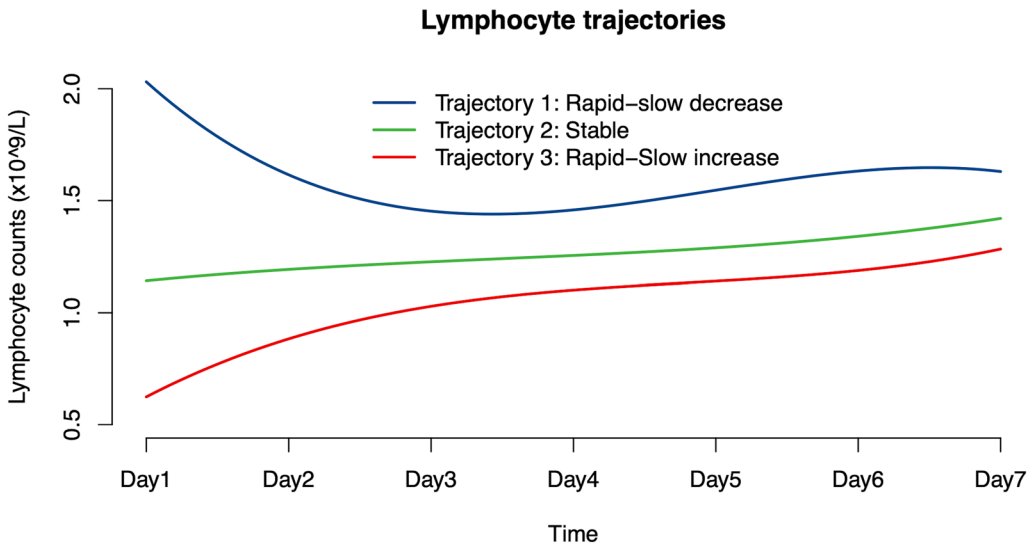

Fig. 1 Lymphocyte trajectories over the first 7 days of ICU admission

Table 1 Baseline characteristics comparison among the three lymphocyte trajectories

Variables	Trajectory 1 (N = 525)	Trajectory 2 (N = 1453)	Trajectory 3 (N = 1174)	p
Age, years	61.0 (47.2–74.1)	64.9 (52.2–78.0)	69.4 (57.6–81.3)	< 0.001
Gender (male), n (%)	255 (48.6%)	821 (56.5%)	727 (61.9%)	< 0.001
Length of hospital, days	9.2 (5.7–14.8)	10.0 (6.1–16.5)	10.1 (6.2–16.7)	0.026
Length of ICU, days	4.1 (2.3–7.8)	4.2 (2.3–8.5)	4.7 (2.5–9.0)	0.065
SOFA	3.0 (2.0–5.0)	3.0 (2.0–4.0)	3.0 (2.0–5.0)	0.026
GCS	15.0 (13.0–15.0)	15.0 (13.0–15.0)	15.0 (13.0–15.0)	0.619
APSIII	52.0 (39.0–68.0)	50.0 (38.0–65.0)	54.0 (43.0–68.0)	< 0.001
OASIS	35.0 (29.0–41.0)	35.0 (29.0–40.0)	37.0 (31.0–42.0)	< 0.001
SRIS	3.0 (3.0–4.0)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	< 0.001
MELD	15.0 (9.0–22.6)	14.8 (9.0–22.3)	17.2 (10.0–24.3)	< 0.001
Charlson comorbidity index	4.0 (2.0–6.0)	4.0 (2.0–6.0)	5.0 (3.0–7.0)	< 0.001
Hospital mortality, n (%)	105 (20%)	233 (16%)	284 (24.2%)	< 0.001
ICU mortality, n (%)	89 (17%)	177 (12.2%)	204 (17.4%)	< 0.001
28-day mortality, n (%)	100 (19%)	216 (14.9%)	269 (22.9%)	< 0.001
7-day mortality, n (%)	63 (12%)	113 (7.8%)	132 (11.2%)	0.002

SOFA, Sequential Organ Failure Assessment; GCS, Glasgow Coma Scale; APSIII, Acute Physiology Score III; OASIS, Oxford Acute Severity of Illness Score; SIRS, Systemic Inflammatory Response Syndrome; MELD, Model for End-stage Liver disease

curves illustrated differences in mortality among trajectories over 28 days (Fig. 2). Consistent with the Cox regression results, Trajectory 1 had the highest mortality within the first 7 days, after which its mortality curve overlapped with that of Trajectory 2, while Trajectory 3 had the highest mortality beyond the 7-day timeframe. Additional subgroup analysis stratified by comorbidities demonstrated no significant interaction between lymphocyte count trajectories and any comorbidities (Figure S1 and Figure S2), indicating that comorbidities did not affect the association between trajectories and patient outcomes.

The distinct lymphocyte trajectories might imply different immune profiles and outcomes in sepsis. Trajectory 1, with initially high lymphocyte counts, was associated with elevated SIRS scores and 7-day mortality, possibly reflecting a pro-inflammatory sepsis phenotype. In contrast, Trajectory 3, with relatively low lymphocyte counts, correlated with higher 28-day mortality, suggesting an immunosuppressive profile. This pattern aligns with prior

Table 2 Univariate and multivariate Cox regression analysis of the three lymphocyte trajectories

Outcome	Trajectory	Crude	Model I	Model II	Model III
28-day mortality	Trajectory 2	Ref	Ref	Ref	Ref
	Trajectory 1	1.33 (1.05–1.68, $p=0.019$)	1.30 (1.03–1.66, $p=0.029$)	1.17 (0.92–1.48, $p=0.212$)	1.22 (0.96–1.55, $p=0.110$)
	Trajectory 3	1.61 (1.34–1.92, $p<0.001$)	1.53 (1.27–1.83, $p<0.001$)	1.34 (1.12–1.61, $p=0.001$)	1.37 (1.14–1.64, $p=0.001$)
7–day mortality	Trajectory 2	Ref	Ref	Ref	ref
	Trajectory 1	1.58 (1.16–2.15, $p=0.004$)	1.22 (0.89–1.66, $p=0.218$)	1.15 (0.84–1.57, $p=0.382$)	1.22 (0.89–1.68, $p=0.219$)
	Trajectory 3	1.47 (1.15–1.89, $p=0.003$)	1.57 (1.22–2.03, $p=0.001$)	1.41 (1.09–1.83, $p=0.008$)	1.54 (1.18–2.00, $p=0.001$)

Model I: adjusted by Age, Gender, Length of hospital, and Length of ICU; Model II: adjusted by Age, Gender, Length of hospital, Length of ICU, SOFA, GCS, APSIII, LODS, OASIS, SAPSII, SRIS, MELD, and Charlson comorbidity index; Model III: adjusted by Age, Gender, Length of hospital, Length of ICU, SOFA, GCS, APSIII, LODS, OASIS, SAPSII, SRIS, MELD, Charlson comorbidity index, Acute kidney injury, Myocardial infarction, Congestive heart failure, Peripheral vascular disease, Cerebrovascular disease, Dementia, Chronic pulmonary disease, Peptic ulcer disease, Mild liver disease, Severe liver disease, Diabetes without chronic complication, Diabetes with chronic complication, and Paraplegia

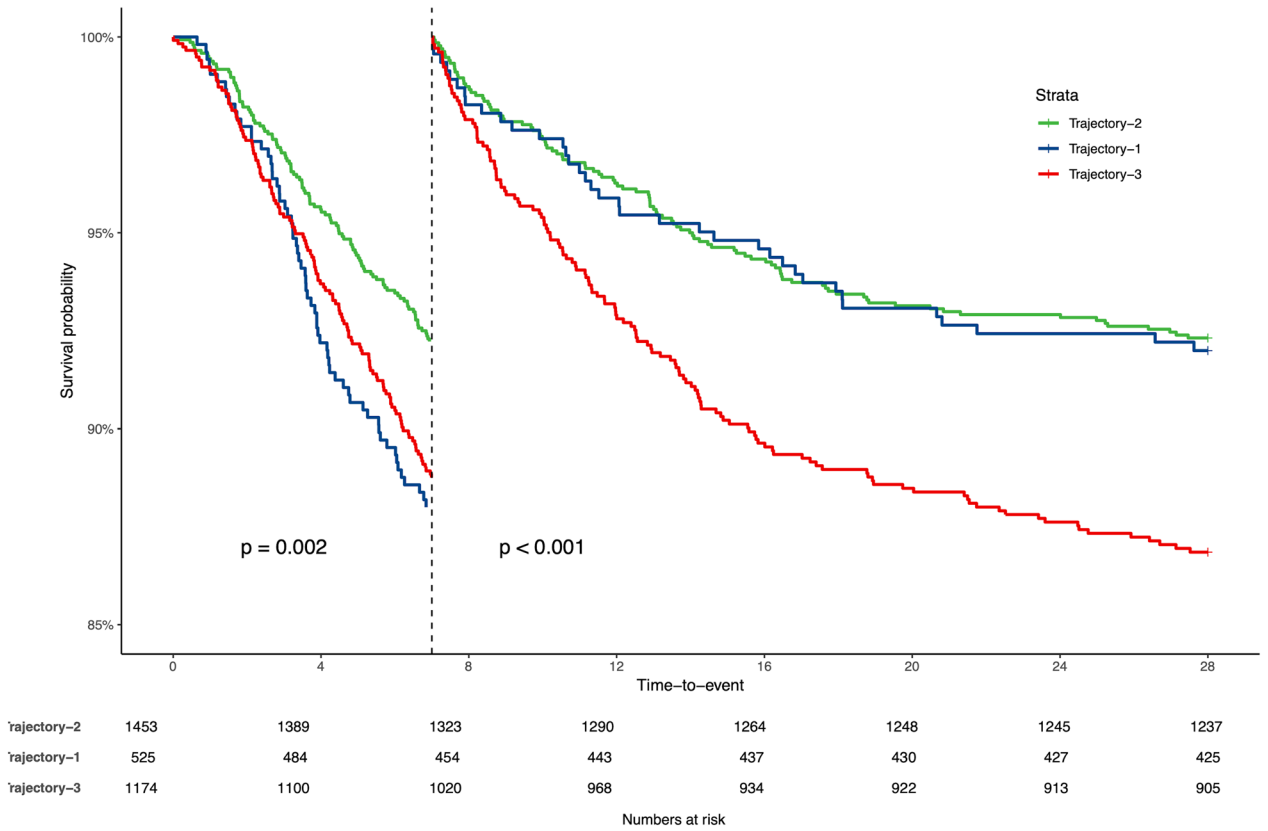

Fig. 2 Kaplan–Meier survival curves of the three trajectories

research indicating that early death in sepsis is driven by intense inflammation, while late death is more commonly associated with immunosuppression [4]. These findings highlight the potential role of tailored therapies for different sepsis subtypes. Specifically, patients with a pro-inflammatory profile (Trajectory 1) may benefit from anti-inflammatory agents like corticosteroids or ulinastatin [5]. For patients with an immunosuppressive profile (Trajectory 3), immune-stimulating therapies such as thymosin α1, which restores lymphocyte counts, or IL-7, which promotes lymphocyte proliferation and prevents apoptosis, might be advantageous [5]. As for patients in the stable profile (Trajectory 2), representing the majority of cases with the lowest mortality, standard, guideline-based supportive care may be sufficient.

In conclusion, three distinct lymphocyte trajectories were identified in sepsis patients using GBTM. Trajectory 3 was a strong predictor of 7-day and 28-day mortality,

while Trajectory 1 was associated with early death. These findings might support the development of more personalized management strategies for sepsis. Future prospective studies could focus on investigating the efficacy of targeted immune therapy on different trajectories to better understand potential interactions between immune therapy and sepsis subgroups.

Abbreviations

ICU	Intensive care unit
HLA-DR	Human leukocyte antigen-DR isotype
GBTM	Group-based trajectory modeling
MIMIC	Medical information mart for intensive care
SOFA	Sequential organ failure assessment
APSIII	Acute physiology score III
OASIS	Oxford acute severity of illness score
SIRS	Systemic inflammatory response syndrome
MELD	Model for end-stage liver disease

Supplementary Information

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Additional file 1

Author contributions

JY contributed to conceptualization, manuscript writing and editing, statistical analysis, and visualization. BM contributed to data collection and statistical analysis. HT contributed to manuscript reviewing and funding acquisition. All authors read and approved the final manuscript.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

Ethic approval and consent to participate

Not applicable. The MIMIC database is publicly available and has been anonymized. No need for further approval from an ethical committee.

Consent for publication

All authors consent for publication.

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