Using Procalcitonin Trajectories to Identify Sepsis Subphenotypes and Risk Stratification: A Postprint

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Abstract

Background Sepsis is a heterogeneous disease, and identifying sepsis subphenotypes contributes to optimizing sepsis management. Objective To utilize procalcitonin (PCT) trajectories to identify sepsis subphenotypes and perform risk stratification. Methods A retrospective analysis was conducted on 800 adult sepsis patients (age $>$ 18 years) admitted to the General Hospital of Ningxia Medical University and 202 adult sepsis patients admitted to Gansu Provincial People's Hospital from January 1, 2021, to August 1, 2023. Patients from the General Hospital of Ningxia Medical University were randomly divided, with 597 patients (60%) assigned to the development cohort and the remaining 203 patients together with the 202 patients from Gansu Provincial People's Hospital (total 405 patients) assigned to the validation cohort (40%). First, based on 28-day survival status, the development cohort was divided into survivor and non-survivor groups to analyze the prognostic value of PCT measurements at different time points for sepsis, and receiver operating characteristic (ROC) curves were plotted to evaluate predictive performance. Then, group-based trajectory modeling based on repeated PCT measurements was performed to identify sepsis subphenotypes, which were characterized according to PCT trends and clinical features, followed by survival analysis and risk stratification. Finally, the predictive model was validated. Results In the development cohort, 512 patients survived and 85 died, with an overall 28-day mortality of 14.2%; in the validation cohort, 341 patients survived and 64 died, with an overall 28-day mortality of 16.3%. In the development cohort, PCTd3, PCTd5, and PCTd7 were higher in the non-survivor group than in the survivor group ($P < 0.01$). ROC curve results showed that PCTd7 had relatively high predictive performance, with an area under the ROC curve of 0.833. Group-based trajectory modeling in the development cohort identified four sepsis subphenotypes: "mid-level rapid rise type" was characterized by respiratory dysfunction; "low-level slow decline

type" was characterized by lower complication rates and critical illness scores, considered as the baseline group; "high-level rapid decline type" was characterized by higher comorbidity and critical illness scores; "high-level slow decline type" was characterized by multiple organ dysfunction and the highest critical illness scores, considered as the most severe group upon admission. Survival analysis of the four subphenotypes revealed that "mid-level rapid rise type" had the highest mortality and was defined as the high-risk group; followed by "high-level slow decline type," defined as the intermediate-risk group; "low-level slow decline type" and "high-level rapid decline type" had lower mortality rates and were defined as low-risk groups. The relative distribution of PCT trajectories and comorbidities in the validation cohort was essentially consistent with that in the development cohort. Conclusion PCT trajectories can be used to identify sepsis subphenotypes, and combining PCT values with their changing trends can enable risk stratification of sepsis, providing a theoretical basis for clinicians to utilize PCT trajectory changes to evaluate patient prognosis.

Full Text

Identification of Sepsis Subphenotypes and Risk Stratification Using the Procalcitonin Trajectory

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Abstract

Background Sepsis is a heterogeneous disease, and identifying sepsis subphenotypes can help optimize sepsis management. **Objective** To identify sepsis subphenotypes and perform risk stratification using procalcitonin trajectories. **Methods** We retrospectively analyzed 800 adult sepsis patients (age >18 years) admitted to the General Hospital of Ningxia Medical University and 202 adult sepsis patients admitted to Gansu Provincial Hospital between January 1, 2021 and August 1, 2023. Patients from the General Hospital of Ningxia Medical University were randomly allocated to a development cohort (597 patients, 60%) and a validation cohort (203 patients). The 202 patients from Gansu Provincial Hospital were combined with these 203 patients to form a total validation cohort

of 405 patients (40%). First, the development cohort was divided into survival and death groups based on 28-day survival status to analyze the prognostic value of procalcitonin measurements at different time points, with ROC curves plotted to assess predictive efficacy. Second, group-based trajectory modeling (GBTM) based on repeated procalcitonin measurements was performed to identify sepsis subphenotypes, which were characterized according to procalcitonin trends and clinical features, followed by survival analysis and risk stratification. Finally, the predictive model was validated. **Results** In the development cohort, 512 patients survived and 85 died, with an overall 28-day mortality of 14.2%. In the validation cohort, 341 patients survived and 64 died, with an overall 28-day mortality of 16.3%. PCT d3, PCT d5, and PCT d7 were significantly higher in the death group than in the survival group ($P<0.01$). ROC curve results showed that PCT d7 had the highest predictive efficacy with an area under the ROC curve of 0.833. GBTM identified four sepsis subphenotypes: "Middle Start Rapid Rise" was characterized by respiratory dysfunction; "Low Start Slow Decline" had the lowest comorbidity and critical care scores and served as the baseline group; "High Start Rapid Decline" was characterized by higher comorbidity and critical care scores; and "High Start Slow Decline" was characterized by multiple organ dysfunction with the highest critical care scores, representing the most severe group on admission. Survival analysis of the four subphenotypes showed that "Middle Start Rapid Rise" had the highest mortality and was defined as the high-risk group, followed by "High Start Slow Decline" as the intermediate-risk group, while "Low Start Slow Decline" and "High Start Rapid Decline" had lower mortality and were defined as low-risk groups. The relative distributions of procalcitonin trajectories and comorbidities were generally consistent between the validation and development cohorts. **Conclusion** Procalcitonin trajectories can be used to identify sepsis subphenotypes, and combining procalcitonin values with trajectories can achieve risk stratification for sepsis, providing a theoretical basis for clinicians to assess patient prognosis using procalcitonin trajectories.

Keywords Sepsis; Procalcitonin; Subphenotype; Group-based trajectory modeling; Prognosis; Survival analysis

Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host response to infection, representing a major public health threat. The persistently high mortality risk is primarily attributed to the intrinsic heterogeneity of sepsis' multidimensional clinical and biological characteristics and the variable individual responses to standardized treatment protocols. This complexity has spurred precision medicine approaches aimed at stratifying patients into more homogeneous cohorts to facilitate novel therapeutic applications, with subphenotype identification being a critical step. Biomarkers for sepsis classification should be affordable, rapidly obtainable, and have low detection error to enable

routine clinical practice. Procalcitonin is widely used as a specific indicator of bacterial infection to assess sepsis severity, though consensus on its prognostic value is lacking. However, procalcitonin clearance is a good predictor of sepsis prognosis, with higher clearance associated with lower mortality risk. Currently, comprehensive assessment of sepsis prognosis combining procalcitonin values and trends has not been extensively studied. This study measured procalcitonin at different time points and used group-based trajectory modeling to identify sepsis subphenotypes, analyze their characteristics, and perform prognostic risk stratification, aiming to evaluate sepsis prognosis using procalcitonin trajectories.

1. Methods

1.1 Study Subjects

We retrospectively analyzed 800 adult sepsis patients (age >18 years) admitted to the General Hospital of Ningxia Medical University and 202 adult sepsis patients admitted to Gansu Provincial Hospital between January 1, 2021 and August 1, 2023. Patients from the General Hospital of Ningxia Medical University were randomly allocated to a development cohort (597 patients, 60%) and a validation cohort (203 patients). The 202 patients from Gansu Provincial Hospital were combined with these 203 patients to form a total validation cohort of 405 patients (40%). All patients met sepsis diagnostic criteria and completed blood cultures and antibiotic intervention within 3 hours of emergency department admission or hospital admission. Exclusion criteria included: non-bacterial pathogens, hospital stay <7 days after sepsis diagnosis with incomplete procalcitonin data, and presence of malignant tumors, hematological disorders, or autoimmune diseases.

1.2 Clinical Data

Clinical data included infection source, comorbidities, gender, age, temperature, heart rate, respiratory rate, blood pressure, white blood cell count, hemoglobin, platelet count, alanine aminotransferase, aspartate aminotransferase, bilirubin, albumin, serum creatinine, blood urea nitrogen, fibrinogen, D-dimer, blood lactate, Glasgow Coma Scale (GCS) score, vasopressor use (including dopamine, epinephrine, norepinephrine), mechanical ventilation, urine output in the first 24 hours, and complications. Laboratory variables represented the most severe values within 24 hours of sepsis diagnosis. Procalcitonin values on days 1, 3, 5, and 7 were recorded as PCT d1, PCT d3, PCT d5, and PCT d7. Sequential Organ Failure Assessment (SOFA) score and Acute Physiology and Chronic Health Evaluation II (APACHE II) score were manually calculated. The endpoint was 28-day mortality based on survival status after sepsis diagnosis.

1.3 Missing Values

Variables with >40% missing values were excluded. Interleukin-6, erythrocyte sedimentation rate, serum amyloid A, and brain natriuretic peptide (BNP) had >40% missing values and were therefore excluded from the study.

1.4 Statistical Methods

Statistical analysis was performed using SPSS 26.0. Normally distributed continuous variables were expressed as mean ± standard deviation and compared between groups using independent samples t-test. Non-normally distributed continuous variables were expressed as median (P25, P75) and compared using Mann-Whitney U test. Receiver operating characteristic (ROC) curves were used to evaluate the prognostic value of procalcitonin for sepsis. Group-based trajectory modeling (GBTM) was conducted using the traj package in Stata 17.0. Model fitting started with a two-group model, gradually increasing the number of groups from higher-order to lower-order functions. Model selection was based on Bayesian Information Criterion (BIC), Akaike Information Criterion (AIC), average posterior probability (AvePP), and entropy. BIC and AIC values closer to 0 indicated better model fit, and AvePP >0.7 indicated acceptable model fit. GraphPad 8.0 was used for statistical analysis and graphing. Kruskal-Wallis test and 2 test were used to define subphenotype characteristics by analyzing demographics, comorbidities, and physiological indicators among trajectory groups. Kaplan-Meier curves were used for survival analysis with Log-rank test for group comparisons.

2. Results

2.1 Patient Characteristics

In the development cohort, 512 patients survived and 85 died, with an overall 28-day mortality of 14.2%. The median SOFA score was 5 (3, 8), median APACHE II score was 13 (10, 19), and median hospital stay was 11 (8, 16) days. In the validation cohort, 341 patients survived and 64 died, with an overall 28-day mortality of 16.3%.

2.2 Prognostic Value of Procalcitonin

Procalcitonin trajectories in both survivor and non-survivor groups showed a declining trend [Figure 1: see original paper]. PCT d3, PCT d5, and PCT d7 were significantly higher in the death group than in the survival group (P<0.01) . ROC curve analysis showed that predictive efficacy for sepsis prognosis increased with hospital stay duration. PCT d7 demonstrated the highest predictive efficacy with sensitivity of 0.812, specificity of 0.742, and area under the ROC curve of 0.833 [TABLE:2, FIGURE:2].

2.3 Group-Based Trajectory Modeling

GBTM of 597 sepsis patients in the development cohort identified that as the number of trajectory groups increased from 2 to 5, AIC and BIC values decreased while entropy increased. When the number of groups reached 5, data were missing. With 4 trajectory groups, AvePP values were 0.99, 0.99, 0.97, and 0.97, all exceeding the empirical standard of 0.70, indicating good model fit . Therefore, four trajectory groups were selected as the final model.

Phenotype 1 (n=14, 2.4%) was characterized by moderate initial values [procalcitonin 23.0 (4.1, 29.3) ng/mL] with a rapid rising trend, reaching the highest value on day 7 [procalcitonin 78.5 (61.8, 89.0) ng/mL], defined as "Middle Start Rapid Rise." Phenotype 2 (n=470, 81.4%) showed the lowest initial values [procalcitonin 9.5 (3.45, 21.9) ng/mL] with a slow declining trend, reaching the lowest value on day 7 [procalcitonin 0.72 (0.28, 1.7) ng/mL], defined as "Low Start Slow Decline." Phenotype 3 (n=83, 13.9%) featured high initial values [procalcitonin 92.0 (66.0, 100.0) ng/mL] with a rapid declining trend, approaching baseline levels on day 7 [procalcitonin 3.9 (1.6, 6.8) ng/mL], defined as "High Start Rapid Decline." Phenotype 4 (n=30, 4.9%) had the highest initial values [procalcitonin 100 (100, 100) ng/mL] with no significant decline from day 1 to day 3, followed by a rapid decline, maintaining relatively high values on day 7 [procalcitonin 22.2 (12.5, 46.5) ng/mL], defined as "High Start Slow Decline" [Figure 3: see original paper].

2.4 Characteristics of Trajectory Groups

Comparative analysis revealed that the "Middle Start Rapid Rise" group had the fewest patients, was oldest, and had the shortest hospital stay, primarily with pulmonary infections and the highest mortality (71.4%). The "Low Start Slow Decline" group had the most patients, was younger, had the shortest ICU stay, with abdominal, pulmonary, and urinary tract infections, and the lowest mortality (11.5%). The "High Start Rapid Decline" group was older with shorter ICU stays, primarily abdominal and urinary tract infections, and lower mortality (12.0%). The "High Start Slow Decline" group was youngest with the longest ICU and total hospital stays, primarily abdominal and urinary tract infections, and higher mortality (36.7%). No significant differences were observed in gender or heart rate among the four phenotypes ($P>0.05$).

Comorbidity analysis showed that "Middle Start Rapid Rise" was characterized by respiratory failure with the highest proportion of severe electrolyte disturbances and lowest rates of leukopenia, thrombocytopenia, hepatic insufficiency, and acute kidney injury. "Low Start Slow Decline" had the lowest proportions of septic shock, hyperlactatemia, and severe electrolyte disturbances. "High Start Rapid Decline" showed generally higher comorbidity rates. "High Start Slow Decline" was characterized by multiple organ dysfunction with the highest rates of thrombocytopenia, hepatic insufficiency, acute kidney injury, ARDS, mechanical ventilation, hyperlactatemia, and septic shock, considered the most

severe group on admission.

Score comparisons showed that “Middle Start Rapid Rise” had the highest APACHE II score and lowest GCS score. “Low Start Slow Decline” had the highest GCS score and lowest SOFA and APACHE II scores. “High Start Slow Decline” had the highest SOFA score .

2.5 Survival Analysis and Risk Stratification

Kaplan-Meier survival analysis of the four sepsis phenotypes showed that survival rates plateaued approximately two weeks after admission. Log-rank test results using “Low Start Slow Decline” as the baseline group demonstrated that “Middle Start Rapid Rise” (2=72.84, P<0.01) and “High Start Slow Decline” (2=18.04, P<0.01) had significantly higher mortality risk, while no significant difference was observed compared with “High Start Rapid Decline” (2=0.01, P=0.906). Additionally, comparison between “Middle Start Rapid Rise” and “High Start Slow Decline” showed that “Middle Start Rapid Rise” had higher mortality risk (2=6.423, P<0.05). Therefore, risk stratification was established: “Middle Start Rapid Rise” as high-risk, “High Start Slow Decline” as intermediate-risk, and “Low Start Slow Decline” and “High Start Rapid Decline” as low-risk groups [Figure 4: see original paper].

2.6 Model Validation

GBTM of the validation cohort also identified four trajectory groups with procalcitonin trajectory characteristics largely consistent with the development cohort [Figure 5: see original paper]. The “Middle Start Rapid Rise” group in the validation cohort had higher repeated procalcitonin measurements than the development cohort but maintained a rapid rising trend, while other phenotypes showed consistent trajectory features. The relative distribution of comorbidities among the four phenotypes was also consistent with the development cohort. In the validation cohort, “Middle Start Rapid Rise” had the highest 28-day mortality (86.7%), followed by “High Start Slow Decline” (33.3%), “High Start Rapid Decline” (12.7%), and “Low Start Slow Decline” (11.6%) . Kaplan-Meier survival analysis of the validation cohort with Log-rank test using “Low Start Slow Decline” as baseline showed that “Middle Start Rapid Rise” (2=113.70, P<0.01) and “High Start Slow Decline” (2=13.29, P<0.01) had significantly higher mortality risk, with no significant difference compared to “High Start Rapid Decline” (2=0.18, P=0.666). Comparison between “Middle Start Rapid Rise” and “High Start Slow Decline” confirmed higher mortality risk in “Middle Start Rapid Rise” (2=21.09, P<0.01). Thus, the validation cohort yielded identical risk stratification: “Middle Start Rapid Rise” as high-risk, “High Start Slow Decline” as intermediate-risk, and “Low Start Slow Decline” and “High Start Rapid Decline” as low-risk groups [Figure 6: see original paper].

3. Discussion

Sepsis is characterized by heterogeneity and immune dysregulation, with no effective treatments currently available, representing a major cause of mortality in ICU patients. This study first utilized repeated procalcitonin measurements for sepsis prognosis assessment, demonstrating that predictive value increased with measurement duration, supporting the use of procalcitonin trajectories for risk stratification. By integrating procalcitonin values and trends, we identified sepsis subphenotypes through GBTM of repeated measurements and performed risk stratification based on patient prognosis.

The four subphenotypes identified through procalcitonin trajectories showed characteristics consistent with their comorbidity profiles and critical illness scores. White blood cell counts, platelet counts, and septic shock incidence also provided evidence of inflammatory status. Clinically, "Middle Start Rapid Rise" was characterized by respiratory dysfunction; "Low Start Slow Decline" had the lowest comorbidities and critical illness scores, serving as the baseline group; "High Start Rapid Decline" featured higher comorbidities and scores but lower mortality; "High Start Slow Decline" was characterized by multiple organ dysfunction with the highest critical illness scores.

Survival analysis revealed "Middle Start Rapid Rise" as the high-risk group, followed by "High Start Slow Decline" as intermediate-risk, while "Low Start Slow Decline" and "High Start Rapid Decline" were low-risk groups. Procalcitonin trajectories showed that "Middle Start Rapid Rise" had initially low but rapidly increasing values, contrasting with "High Start Slow Decline's" high initial values with slow decline, indicating that rising procalcitonin and failure to clear predict high mortality in sepsis, consistent with Liu et al. Comparing "High Start Slow Decline" and "High Start Rapid Decline," both had high initial procalcitonin values and multiple organ dysfunctions, but "High Start Slow Decline" had significantly higher mortality. Trajectory analysis showed "High Start Rapid Decline" had a more pronounced procalcitonin decrease, indicating better infection control and explaining its better prognosis, consistent with previous studies. Comparison of 30% and 50% procalcitonin decline rates between these two phenotypes confirmed significantly higher decline rates in "High Start Rapid Decline," demonstrating that rapid procalcitonin decrease improves survival.

Comparison between "High Start Rapid Decline" and "Low Start Slow Decline" showed no mortality difference, with "Low Start Slow Decline" having the lowest initial procalcitonin and stable trajectory, suggesting that procalcitonin clearance rate impacts prognosis more than absolute values, consistent with Karlsson et al. This also indicates that initial procalcitonin measurement only reflects admission severity rather than predicting prognosis, supporting our findings and consistent with Sager et al. Both phenotypes had low PCT d7 values without significant differences, indicating good prognosis.

Model validation showed procalcitonin trajectories and comorbidity distribu-

tions were consistent with the development cohort. The validation cohort's "Middle Start Rapid Rise" group had higher procalcitonin values but maintained the rapid rising trend, confirming high mortality characteristics. The higher proportion of pulmonary infections in this phenotype further validates the high mortality of pulmonary sepsis, suggesting that patient allocation proportions in specific phenotypes may cause relative differences in outcomes.

Limitations include using 28-day mortality as the endpoint without long-term follow-up. Additionally, system limitations precluded inclusion of cytokine and immunological markers. However, we excluded viral and other non-bacterial sepsis patients, making procalcitonin appropriate for assessing infection severity. Finally, risk stratification using repeated procalcitonin measurements has some lag, requiring integration with scoring systems.

In conclusion, procalcitonin trajectories can identify sepsis subphenotypes, and combining procalcitonin values with trajectories enables risk stratification, providing a theoretical basis for clinicians to assess patient prognosis using procalcitonin trajectories.

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Author Contributions: ZHANG Shaotong was responsible for research design and manuscript drafting; WANG Bo performed statistical analysis and graph preparation; ZHANG Mingrui and MA Guiyan were responsible for data collection and statistical analysis; LIU Shaoguang was responsible for research design, quality control, and overall article supervision.

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Note: Figure translations are in progress. See original paper for figures.