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Novel cortisol trajectory sub-phenotypes in sepsis

Fei Leng[1†], Zhunyong Gu[1†], Simeng Pan[1], Shilong Lin[1], Xu Wang[1], Ming Zhong[1*] and Jieqiong Song[1*]

Abstract

Background Sepsis is a heterogeneous syndrome. This study aimed to identify new sepsis sub-phenotypes using plasma cortisol trajectory.

Methods This retrospective study included patients with sepsis admitted to the intensive care unit of Zhongshan Hospital Fudan University between March 2020 and July 2022. A group-based cortisol trajectory model was used to classify septic patients into different sub-phenotypes. The clinical characteristics, biomarkers, and outcomes were compared between sub-phenotypes.

Results A total of 258 patients with sepsis were included, of whom 186 were male. Patients were divided into two trajectory groups: the lower-cortisol group (n = 217) exhibited consistently low and slowly declining cortisol levels, while the higher-cortisol group (n = 41) showed relatively higher levels in comparison. The 28-day mortality (65.9% vs.16.1%, $P < 0.001$) and 90-day mortality (65.9% vs. 19.8%, $P < 0.001$) of the higher-cortisol group were significantly higher than the lower-cortisol group. Multivariable Cox regression analysis showed that the trajectory sub-phenotype (HR = 5.292; 95% CI 2.218–12.626; $P < 0.001$), APACHE II (HR = 1.109; 95% CI 1.030–1.193; $P = 0.006$), SOFA (HR = 1.161; 95% CI 1.045–1.291; $P = 0.006$), and IL-1β (HR = 1.001; 95% CI 1.000–1.002; $P = 0.007$) were independent risk factors for 28-day mortality. Besides, the trajectory sub-phenotype (HR = 4.571; 95% CI 1.980–10.551; $P < 0.001$), APACHE II (HR = 1.108; 95% CI 1.043–1.177; $P = 0.001$), SOFA (HR = 1.270; 95% CI 1.130–1.428; $P < 0.001$), and IL-1β (HR = 1.001; 95% CI 1.000–1.001; $P = 0.015$) were also independent risk factors for 90-day mortality.

Conclusion This study identified two novel cortisol trajectory sub-phenotypes in patients with sepsis. The trajectories were associated with mortality, providing new insights into sepsis classification.

Keywords Sepsis, Cortisol, Sub-phenotype, Trajectory, Mortality

Introduction

Sepsis is a life-threatening organ dysfunction caused by a dysregulated host response to infection [1]. The course of sepsis is highly heterogeneous due to different causal agents, patient conditions, comorbidities, and treatments, resulting in highly variable patient outcomes with the same treatments in different septic patients [2]. Consequently, identifying patient subgroups precisely is crucial to optimize sepsis treatment and improve prognosis.

Despite significant advances in modern medicine, accurately assessing the severity and effectively predicting the prognosis of sepsis remains a major challenge. Sepsis is a dynamic condition that exhibits different biological responses over minutes to hours [3, 4], and static laboratory tests often fail to recognize sepsis sub-phenotypes that evolve [5, 6]. Group-based trajectory modeling (GBTM) has become an important topic in the field of

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critical care as a new phenotypic grouping tool that can be used to analyze potential categories using changes in indicators in the time dimension [7–9]. Recent studies on sepsis sub-phenotypes utilizing the GBTM approach have incorporated routinely accessible clinical variables, such as inflammation factors [10] and vital signs [7, 9].

Sepsis is associated with an abnormal response of the hypothalamic–pituitary–adrenal (HPA) axis [11]. Cytokines (including IL-1, IL-6, and TNF-α) stimulate the HPA axis, increasing the secretion of corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH) [12, 13]. The body can counteract the inflammatory response by activating the HPA axis to increase cortisol levels [14, 15], which has immunosuppressive effects, decreases cytokine concentrations, and maintains vascular tension, catecholamine sensitivity, and endothelial integrity [15]. Nevertheless, with sepsis progression, the typical cortisol secretion and feedback mechanisms of the HPA axis can be disturbed, and critical illness-related corticosteroid insufficiency (CIRCI) may occur, leading to uncontrolled inflammatory responses and disturbed circadian rhythms [12]. Therefore, in patients with sepsis, cortisol levels are highly heterogeneous [14].

The current understanding regarding whether the cortisol trajectory in septic patients can be used to identify sepsis sub-phenotypes remains unclear. This study aimed to investigate a novel plasma cortisol trajectory to identify new sepsis sub-phenotypes.

Methods

Study design and patients

This retrospective study included patients diagnosed with sepsis at the intensive care unit (ICU) of Zhongshan Hospital Fudan University between March 2020 and July 2022. Sepsis was diagnosed according to the third international consensus definition of sepsis [16]. The study was approved by the Ethics Committee of Zhongshan Hospital, Fudan University (#B2021-501R). The requirement for informed consent was waived by the committee. The exclusion criteria were as follows: (1) < 18 years old, (2) ICU stay < 72 h, (3) pregnancy, (4) history of corticosteroid treatment or with drugs that affect adrenal function during hospitalization or within 1 year period before admission, or (5) pituitary or adrenal gland abnormalities.

Data collection and outcome

The demographic and clinical characteristics of the patients, including age, sex, acute physiology and chronic health status score II (APACHE II) [17], SOFA score [18], body mass index (BMI), the source of infection at ICU admission, and comorbidities were collected within the first 24 h after admission to the ICU. Laboratory data were collected from the patient charts, including blood routine examination, C-reaction protein (CRP), procalcitonin (PCT), tumor necrosis factor-α (TNF-α), interleukins (ILs), albumin (Alb), creatinine (Cr), alanine transaminase (ALT), aspartate aminotransferase (AST). All biochemical measurements were performed at the Clinical Chemistry Laboratory of the study hospital.

Routine twice-daily cortisol screenings were conducted at 08:00 and 16:00 for all sepsis patients in our ICU to monitor potential variations in cortisol levels and rhythms. To minimize disturbances to patients' sleep, midnight data were not collected. The cortisol levels measured at 08:00 and 16:00 during the first 3 days following sepsis diagnosis were defined as T1 to T6, respectively. Specifically, T1 refers to 08:00 on the first day after sepsis diagnosis, T2 to 16:00 on the same day, T3 to 08:00 on the second day, T4 to 16:00 on the second day, T5 to 08:00 on the third day, and T6 to 16:00 on the third day. All patients were followed for 90 days from ICU admission. The primary outcome of the present study was the 28-day mortality. The secondary outcomes were the 90-day mortality, the duration of mechanical ventilation, and the length of ICU and hospital stays.

Statistical analysis

The GBTM to establish the distinct trajectories of cortisol was conducted using the TRAJ package for Stata 17.0 (StataCorp LP, College Station, TX, USA) [19]. This model [20] delineates the dynamics between cortisol concentrations and time across various trajectories. The calculated likelihoods were termed posterior probabilities of group affiliation. Based on the array of cortisol measurements, the patients were categorized into the trajectory sub-phenotype for which they had the highest probability of group membership. The determination of the ideal count of latent groups within a preferred grouping was influenced by multiple factors [7]. Firstly, enhanced model fit correlates with increased log-likelihood ratios and higher entropy values, the latter maintaining a threshold of no less than 0.7. Secondly, optimal model fit was associated with reduced values of the Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and the sample-size corrected BIC [21]. Thirdly, a critical criterion was that each identified group's average posterior probability (AvePP) had to meet or exceed 70%. Fourthly, each identified category constituted at least 1% of the overall sample volume. Lastly, the ability of the model to be clinically interpretable was an essential consideration.

The statistical analyses were all performed using SPSS 22.0 (IBM, Armonk, NY, USA), R 4.2.1 (Thermo Fisher Scientific, Waltham, MA, USA), or GraphPad Prism 8.0.2

(GraphPad Software Inc., San Diego, CA, USA). Normally distributed continuous variables were described as means ± standard deviations (SDs). Medians and interquartile ranges (IQRs) were used for the continuous variables that were non-normally distributed. Depending on their distributions, between-group comparisons were performed using parametric (Student's t-test) or nonparametric tests (Mann–Whitney U-test). Categorical variables were described as n (%), with intergroup comparisons conducted using the chi-squared test or Fisher's exact test. Univariable and multivariable Cox proportional hazard models were constructed to identify the factors associated with 28- and 90-day mortalities. The variables that were significant in the univariable were included in the multivariable Cox regression analyses. The 28- and 90-day cumulative survival probability was examined using the Kaplan–Meier method. Subgroup analysis was conducted for sex, age, BMI, with or without high blood pressure (HBP), diabetes mellitus (DM), and coronary artery disease (CAD). Multiple imputation (MI) based on five imputed data sets was used to address the missing data with SPSS 22.0 (IBM, Armonk, NY, USA). Statistical significance was determined by two-sided $P < 0.05$.

Results

From March 2020 to July 2022, 3986 patients were admitted to the ICU, of which 457 were diagnosed with sepsis. According to the exclusion criteria, 199 patients were excluded: 11 were < 18 years old, 72 stayed in the ICU < 72 h, 18 were pregnant, 72 had corticosteroid treatment or drugs that affect adrenal function, and 26 had a history of pituitary or adrenal gland abnormalities. Therefore, 258 patients were included in this study. The missing data rate was 1.04% (Supplementary Table 1).

Cortisol trajectories and model adequacy

Two cortisol trajectories were identified using a GBTM approach. The lower-cortisol group included 217 patients (84%), and the higher-cortisol group consisted of 41 patients (16%). The cortisol levels in the lower-cortisol group persisted at a relatively low starting level with a slow and steadily decreasing trend. On the other hand, the cortisol levels in the higher-cortisol group were elevated noticeably at the beginning (> 1500 nmol/L), had sustained high levels at T2-4, and a rapid decrease at T5-6 but remained significantly higher than in the lower-cortisol group (Fig. 1). Model adequacy was evaluated. The entropy value was 0.906 (expected > 0.7 for adequacy). The levels of AIC and BIC were the lowest. The AvePP of the two trajectories were 98% and 92%, respectively (expected > 70% for adequacy). Finally, the ability of the trajectory model was clinically interpretable.

Clinical characteristics and biomarker comparison

No significant differences were observed between the trajectory groups in age, sex, BMI, comorbidity, blood routine, liver or kidney function (all $P > 0.05$). Compared with the lower-cortisol group, patients in the higher-cortisol group showed significantly higher SOFA scores ($P < 0.001$) and APACHE II scores ($P = 0.001$), PCT ($P = 0.004$), TNF-α ($P < 0.001$), IL-6 ($P = 0.007$), IL-1β ($P = 0.004$), IL-10 ($P < 0.001$), and IL-8 ($P = 0.003$) (Table 1).

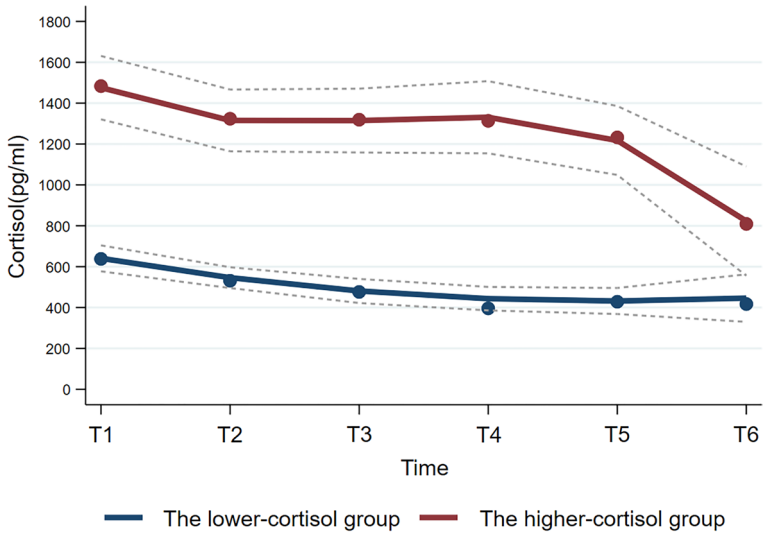

Fig. 1 Group-based trajectory modeling of cortisol levels in septic patients. The dotted gray line represents the 95% confidence interval

Table 1 Characteristics of the patients according to the trajectory

Variable	The lower-cortisol group (n = 217)	the higher-cortisol group (n = 41)	*P*
Age (years)	66.9 ± 15.0	67.5 ± 15.1	0.833
Sex, n (%)			0.850
Male	157 (72.4%)	29 (70.7%)	
Female	60 (27.6%)	12 (29.3%)	
BMI (kg/m^2)	23.2 ± 3.6	23.0 ± 3.7	0.732
Source of infection, n (%)			0.463
Abdominal infection	178 (82.0%)	34 (82.9%)	
Thoracic or lung infections	31 (14.3%)	5 (12.2%)	
Soft tissue and skin infection	4 (1.8%)	0%	
Intracranial infection	4 (1.8%)	2 (4.9%)	
Comorbidity (%)			
High blood pressure	33.2%	24.4%	0.272
Diabetes mellitus	14.3%	17.1%	0.643
Coronary artery disease	11.1%	4.9%	0.387
Kidney dysfunction	3.7%	9.8%	0.103
APACHE II	16 (12–20)	21 (15–24.5)	0.001
SOFA	6 (5–9)	9.5 (7–11)	< 0.001
WBC (× 10^9/L)	12.78 ± 9.34	10.96 ± 9.41	0.257
Lym (× 10^9/L)	0.88 ± 0.67	0.63 ± 0.49	0.210
Neu (× 10^9/L)	11.62 ± 9.8	9.88 ± 8.87	0.294
RBC (× 10^{12}/L)	3.34 ± 0.73	3.30 ± 0.91	0.846
Hb (g/L)	108.0 ± 25.4	107.1 ± 29.3	0.831
PLT (× 10^9/L)	171.2 ± 103.8	153.1 ± 114.6	0.315
CRP (mg/L)	130.5 ± 112.4	111.6 ± 114.3	0.380
PCT (ng/mL)	20.8 ± 26.2	27.8 ± 23.4	0.004
TNF-α (pg/mL)	24.3 (14.8–36.7)	35.4 (25–59.9)	< 0.001
IL-6 (pg/mL)	193 (74.7–715)	741 (140–1000)	0.007
IL-1β (pg/mL)	5 (5–16.3)	9.2 (5–55)	0.004
IL-10 (pg/mL)	12.5 (7–26)	48.6 (25.5–116)	< 0.001
IL-8 (pg/mL)	81.5 (45–247)	189 (86–466)	0.003
Alb (g/L)	30.2 ± 5.2	31.5 ± 5.4	0.367
Cr (mg/dL)	100 (72.5–194.5)	104 (77–179)	0.916
ALT (U/L)	29 (19–73.5)	27 (19–46)	0.293
AST (U/L)	44 (26–118)	41 (25–60.5)	0.315
MV duration (h)	33 (10–102)	50 (29–131)	0.191
Length of hospital stay (days)	16 (10.5–27)	15 (8.25–20)	0.243
Length of ICU stay (days)	5 (3–13.5)	6 (3–12.75)	0.494
28-day mortality, n (%)	35 (16.1%)	27 (65.9%)	< 0.001
90-day mortality, n (%)	43 (19.8%)	27 (65.9%)	< 0.001

BMI, body mass index; APACHE II, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; WBC, white blood cell count; Lym, lymphocyte; Neu, neutrophils; RBC, red blood cell count; Hb, hemoglobin; PLT, platelet; CRP, C-reactive protein; PCT, procalcitonin; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; IL-1β, interleukin-1β; IL-10, interleukin-10; IL-8, interleukin-8; Alb, albumin; Cr, creatinine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; MV, mechanical ventilation; ICU, intensive care unit

Mortality and patient outcomes

There were no significant differences in the duration of mechanical ventilation, the length of ICU, or hospital stay between the two groups. The 28-day mortality (65.9% vs. 16.1%, HR = 5.140; 95% CI 2.426–10.890, $P < 0.001$) and 90-day mortality (65.9% vs. 19.8%, HR = 5.037; 95% CI 2.388–10.620, $P < 0.001$) of the patients in the higher-cortisol group was significantly higher than in the lower-cortisol group (Table 1 and Fig. 2).

Independent influence factors of 28-day and 90-day mortality

Univariable analysis revealed that the trajectory sub-phenotype was significantly associated with both 28-day mortality (HR = 6.152; 95% CI 3.698–10.235; $P < 0.001$) and 90-day mortality (HR = 5.129; 95% CI 3.156–8.335; $P < 0.001$). Other significant factors for 28-day mortality included APACHE II, SOFA, MV duration, length of hospital stay, IL-1β, and IL-10. Significant factors for 90-day mortality included BMI, APACHE II, SOFA, MV duration, ICU days, and IL-1β (all $P < 0.05$) (Table 2). Multivariable Cox regression analysis showed that the trajectory sub-phenotype (HR = 5.292; 95% CI 2.218–12.626; $P < 0.001$), APACHE II (HR = 1.109; 95% CI 1.030–1.193; $P = 0.006$), SOFA (HR = 1.161; 95% CI 1.045–1.291; $P = 0.006$), and IL-1β (HR = 1.001; 95% CI 1.000–1.002; $P = 0.007$) were independent risk factors for 28-day mortality. Besides, the trajectory sub-phenotype (HR = 4.571; 95% CI 1.980–10.551; $P < 0.001$), APACHE II (HR = 1.108; 95% CI 1.043–1.177; P = 0.001), SOFA (HR = 1.270; 95% CI 1.130–1.428; $P < 0.001$), and IL-1β (HR = 1.001; 95% CI 1.000–1.001; P = 0.015) were also independent risk factors for 90-day mortality (Table 2).

Subgroup analysis

The subgroup analyses included all 258 patients revealed that the cortisol trajectory sub-phenotype remained a significant risk factor for 28- and 90-day mortality after stratification by sex, age, BMI, and HBP (all $P < 0.05$) (Fig. 3). A gender subgroup analysis was performed to mitigate concerns regarding generalizability due to gender bias. In the male and female subgroups, the cortisol trajectory subtype grouping still exhibited statistically significant differences in HR for 28- and 90-day mortality, unaffected by gender (Fig. 3).

Discussion

The study identified two distinct sepsis sub-phenotypes based on plasma cortisol trajectory, revealing that patients in the higher-cortisol group had significantly higher 28-day and 90-day mortality rates compared to those in the lower-cortisol group. Cortisol trajectory

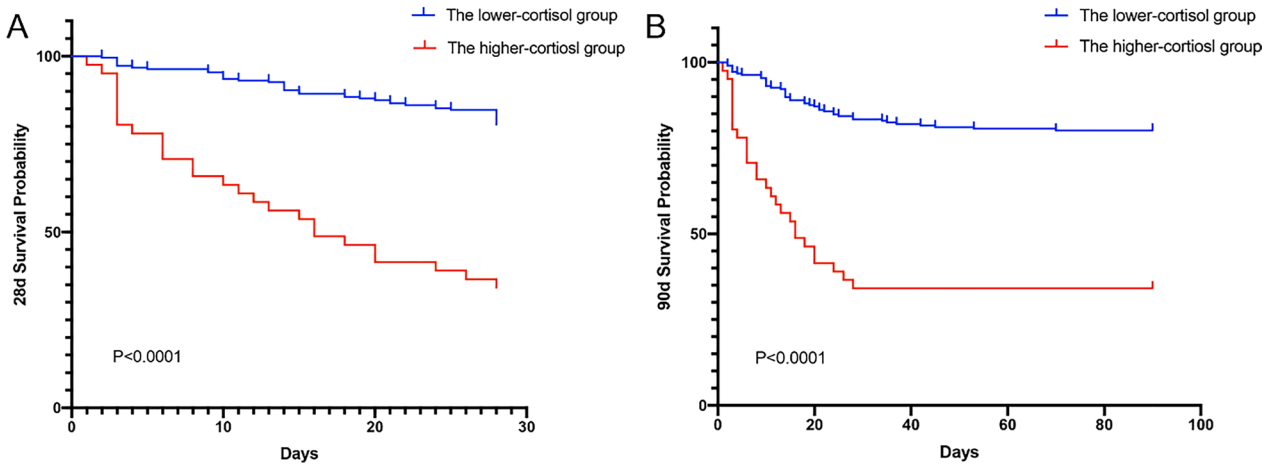

Fig. 2 The 28-day survival probability curve (**A**) and the 90-day survival probability curve (**B**) of patients between the two sub-phenotypes

sub-phenotype was identified as an independent predictor of mortality, highlighting their potential utility in guiding treatment strategies in sepsis management. This study is the first to use GBTM to identify two distinct cortisol trajectory sub-phenotypes in septic patients. This finding provides new insights into the dynamic role of cortisol in sepsis.

Previous studies have shown that critically ill patients, especially those with sepsis, have a disruption of the normal organization of the HPA axis, which may result in an excessive increase in plasma cortisol and correlate with disease severity [12, 22]. In addition, increased blood bile acid concentrations in critically ill patients may inhibit cortisol metabolizing enzymes, leading to increased cortisol [23]. A downregulation of glucocorticoid receptors (GR) activity can also result in glucocorticoid resistance, which may cause an increase in sepsis mortality [24]. Cortisol rhythms are disrupted, and circadian rhythms are lost in patients with sepsis [14]. Still, the exact rhythmic trajectory is unknown, and few studies were reported about cortisol trajectory sub-phenotypes in sepsis. The literature suggests that the need for longitudinal data trajectories may be more helpful in effectively differentiating sub-phenotypes rather than values at individual time points for the more complex factors in patients with sepsis [7, 25].

In the present study, the higher-cortisol group was associated with a significantly higher 28- and 90-day mortality compared with the lower-cortisol group. The present study also showed that the trajectory group, APACHE II score, SOFA score, and IL-1β were independent risk factors for 28- and 90-day mortality. The high mortality is consistent with the high inflammatory state that leads to excessive activation of the necroinflammatory cell death pathways in multiple organs [26, 27] or may be due to unresolved inflammation or immune suppression [28, 29]. Meanwhile, cytokines involved in immune dysregulation play an important role in patients with sepsis, among which IL-1β acts as a pro-inflammatory cytokine, causing organ destruction in sepsis and activating inflammatory vesicles (including NLRP3 in macrophages and endothelial cells) [30]. In addition, macrophage-produced IL-1β destabilizes the vasculature, which further induces inflammatory progression and tissue damage [31]. It is also possible that cytokines directly affect the adrenal glands and regulate cortisol secretion [32, 33], which may be responsible for persistently high cortisol levels. Further understanding of the pathophysiology and biological mechanisms underlying these sub-phenotypes could be crucial for developing the next generation of management strategies for sepsis [34]. Notably, in our study's higher-cortisol group, no deaths were observed between 28 and 90 days of follow-up. The absence of mortality events after day 28 in the higher-cortisol group may be attributed to the following reasons. First, the patients in the higher-cortisol group were generally more critically ill, resulting in a higher risk of mortality within the initial 28 days, with a mortality rate of 65.9%. Consequently, the most critically ill patients tended to succumb early, leading to no additional deaths between days 28 and 90 in this group [35–37]. Second, the small sample size could be involved, as mentioned in the limitations.

The HR for the cortisol trajectory sub-phenotype in the present study was significantly higher than the HR of the APACHE II score, which is known to predict the prognosis of critically ill patients and patients with sepsis [38, 39]. It suggests that the cortisol trajectory group may be more valuable for discriminating the differences in the heterogeneity of sepsis and may serve as a

Table 2 Cox univariate and multivariate regression of 28- and 90-day mortality

Variables	28-day mortality				90-day mortality			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*	HR (95% CI)	*P*
Trajectory sub-phenotype	6.152 (3.698–10.235)	< 0.001	5.292 (2.218–12.626)	< 0.001	5.129 (3.156–8.335)	< 0.001	4.571 (1.980–10.551)	< 0.001
Sex (%)	0.829 (0.463–1.484)	0.528			0.748 (0.428–1.307)	0.308		
Age (years)	0.995 (0.979–1.012)	0.573			0.995 (0.979–1.010)	0.995		
BMI (kg/m^2)	0.949 (0.893–1.008)	0.092			0.939 (0.890–0.991)	0.022		
Source of infection, n (%)	1.410 (0.983–2.021)	0.062			1.379(0.974–1.952)	0.070		
High blood pressure	1.332 (0.747–2.339)	0.337			1.182(0.704–1.986)	0.527		
Diabetes mellitus	1.002 (0.494–2.033)	0.996			1.082(0.568–2.059)	0.811		
Coronary artery disease	0.417 (0.131–1.332)	0.140			0.357(0.112–1.136)	0.357		
Kidney dysfunction	1.005 (0.528–2.075)	0.472			1.093(0.672–2.093)	0.592		
APACHEII	1.109 (1.071–1.149)	< 0.001	1.109 (1.030–1.193)	0.006	1.118 (1.081–1.155)	< 0.001	1.108 (1.043–1.177)	0.001
SOFA	1.186 (1.120–1.256)	< 0.001	1.161 (1.045–1.291)	0.006	1.179 (1.118–1.244)	< 0.001	1.270 (1.130–1.428)	< 0.001
MV (hours)	1.001 (1.000–1.002)	0.045			1.002 (1.001–1.002)	< 0.001		
Length of hospital stay (days)	0.977 (0.957–0.998)	0.030			0.999 (0.987–1.012)	0.936		
ICU days (days)	1.001 (0.983–1.018)	0.961			1.015 (1.004–1.026)	0.009		
WBC (×10^9/L)	0.987 (0.958–1.017)	0.384			0.993 (0.967–1.019)	0.586		
Neu (×10^9/L)	0.984 (0.954–1.015)	0.300			0.990 (0.963–1.017)	0.450		
Lym (×10^9/L)	1.096 (0.929–1.292)	0.277			1.100 (0.942–1.287)	0.234		
Hb (g/L)	0.996 (0.986–1.006)	0.453			0.994 (0.984–1.037)	0.198		
PLT (×10^9/L)	1.0001 (0.997–1.002)	0.713			0.999 (0.997–1.002)	0.531		
CRP (mg/L)	1.001 (0.999–1.004)	0.309			1.002 (0.999–1.004)	0.199		
PCT (ng/mL)	0.999 (0.990–1.009)	0.892			1.003 (0.996–1.011)	0.351		
TNF-α (pg/mL)	1.013 (1.007–1.019)	< 0.001			1.002 (0.993–1.015)	0.432		
IL-6 (pg/mL)	1.000 (0.997–1.001)	0.073			1.001 (1.000–1.001)	0.075		
IL-1β (pg/mL)	1.003 (1.000–1.005)	< 0.001	1.001 (1.000–1.002)	0.007	1.002 (1.000–1.006)	< 0.001	1.001 (1.000–1.001)	0.015
IL-10 (pg/mL)	1.002 (1.000–1.004)	0.037			1.002 (0.991–1.011)	0.078		
IL-8 (pg/mL)	1.000 (0.998–1.001)	0.123			1.000 (1.000–1.070)	0.197		
ALT (U/L)	1.000 (0.999–1.001)	0.680			1.000 (0.999–1.001)	0.656		
AST (U/L)	1.000 (0.999–1.002)	0.497			1.000 (0.999–1.001)	0.587		
Alb (g/L)	0.959 (0.879–1.046)	0.341			0.962 (0.884–1.048)	0.337		
Cr (μmol/L)	1.003 (0.999–1.005)	0.365			0.981 (0.825–1.005)	0.378		

BMI, body mass index; APACHE II, acute physiology and chronic health evaluation; SOFA, sequential organ failure assessment; MV, mechanical ventilation; ICU, intensive care unit; WBC, white blood cell count; Neu, neutrophils; Lym: Hb, hemoglobin; PLT, platelet; CRP, C-reactive protein; PCT, procalcitonin; TNF-α, tumor necrosis factor-α; IL-6, interleukin-6; IL-1β, interleukin-1β; IL-10, interleukin-10; IL-8, interleukin-8; ALT, alanine aminotransferase; AST, aspartate aminotransferase; Alb, albumin; Cr, creatinine

reference for the classification of future sepsis treatments. Current sepsis management guidelines [1, 40–42] do not provide recommendations for precise treatment based on cortisol levels, underscoring the potential for further research into cortisol trajectories in sepsis. For instance, we hypothesize that patients with a high cortisol trajectory might not require corticosteroid therapy, at least not in the early stages, whereas those with a low cortisol trajectory may benefit from earlier and more aggressive corticosteroid treatment. This study may offer some initial insights into the development of more precise, individualized corticosteroid therapy strategies for heterogeneous conditions. Still, how the management of the two subtypes could be optimized requires further studies. The subgroup analysis showed that high cortisol levels (i.e., the higher-cortisol group) indicated high mortality regardless of sex, age, BMI, or HBP, suggesting that the cortisol trajectory grouping is a potentially

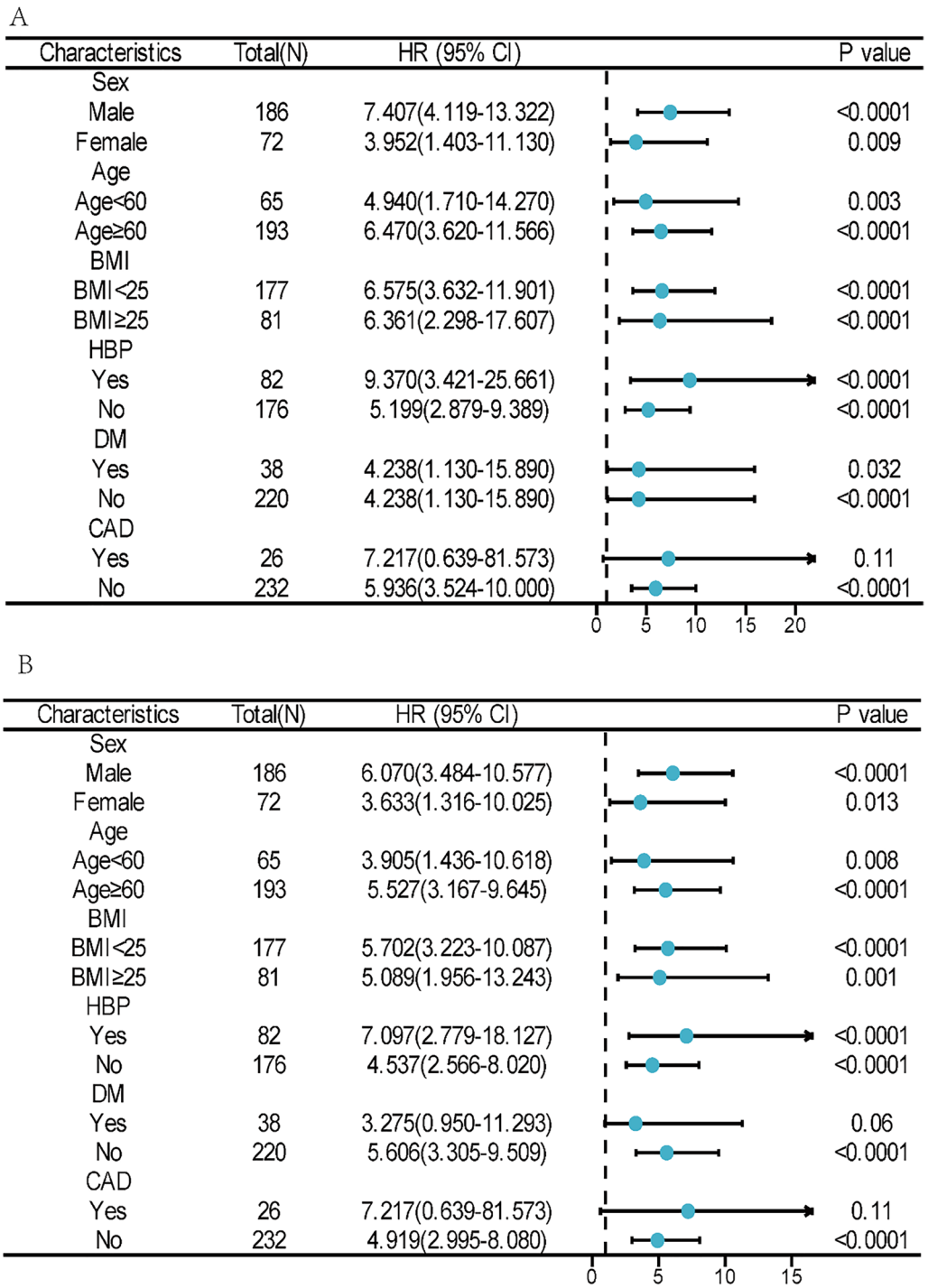

Fig. 3 Forest plots of subgroup analysis for 28-day mortality (**A**) and 90-day mortality (**B**) of the cortisol trajectory group. BMI, Body mass index; HBP, High blood pressure; DM, Diabetes mellitus; CAD, Coronary artery disease

superior sepsis subgroup indicator. Nevertheless, accurately assessing the severity and effectively predicting the prognosis of sepsis remains a major challenge. The significance of the identified sub-phenotypes lies in the potential need to adjust corticosteroid therapy strategies based on different cortisol trajectories to optimize the therapeutic outcomes.

Currently, there are various methods for classifying sepsis trajectory sub-phenotypes. Trajectories based on body temperature (hyperthermic, slow resolvers; hyperthermic, fast resolvers; normothermic; hypothermic) have been shown to distinguish between sepsis sub-phenotypes and are associated with mortality, with the highest mortality observed in hypothermic patients [8, 9, 25]. Bhavani et al. [7] proposed four sepsis sub-phenotypes based on vital sign trajectories, which were associated with different treatment responses. Xu et al. [34] established four trajectories based on SOFA scores: rapidly worsening, delayed worsening, rapidly improving, and delayed improving, all of which were associated with mortality. Additionally, another classification based on the frequency of infections before sepsis was linked to mortality [43]. This study is the first to identify trajectory sub-phenotype in sepsis patients from the perspective of cortisol, providing valuable insights into existing dynamic models. However, a comprehensive comparison of these different trajectories is still lacking, and direct comparisons among studies are challenging due to patient heterogeneity. Future research should aim to concurrently examine multiple trajectories within the same cohort to identify which provides the most accurate associations with patient outcomes.

This study has limitations. Firstly, it was a retrospective single-center study with a limited sample size, resulting in limited generalizability. Secondly, this study only included cortisol measurements twice daily, and the absence of midnight cortisol measurement may have biased the results. Thirdly, due to excluding patients treated with corticosteroids, there is a lack of exploration into the responsiveness to corticosteroid therapy during different cortisol trajectory sub-phenotype patients. Fourthly, patients with ICU stays of less than 72 h were not included, which may limit the generalizability of our conclusions. Therefore, future studies need to be prospective, with more rigorous designs, larger sample sizes, and more comprehensive time rhythm data to validate these results.

In conclusion, this study identified two distinct sepsis sub-phenotypes using plasma cortisol trajectory. The lower-cortisol group exhibited consistently low and slowly declining cortisol levels, while the higher-cortisol group showed relatively higher levels than the lower-cortisol group. A novel cortisol trajectory sub-phenotype was identified as an independent predictor of mortality, providing new insights into sepsis classification and highlighting its potential in treatment strategies for sepsis management.

Supplementary Information

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Supplementary Material 1.

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Not applicable.

Author contributions
Leng Fei and Gu Zhunyong carried out the studies, participated in collecting data, and drafted the manuscript. Pan Simeng, Lin Shilong and Wang Xu performed the statistical analysis and participated in its design. Song Jieqiong and Zhong Ming participated in acquisition, analysis, or interpretation of data and draft the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials
All data generated or analysed during this study are included in this published article.

Declarations

Ethics approval and consent to participate
All procedures were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. This study was approved by the Ethics Committee of the Zhongshan Hospital Fudan University [B2021-501R]. The requirement for individual Informed consent was waived by the Ethics Committee of the Zhongshan Hospital Fudan University because of the retrospective nature of the study. The study was carried out in accordance with the applicable guidelines and regulations.

Consent for publication
Not Applicable.

Competing interests
The authors declare no competing interests.

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References

1. Evans L, Rhodes A, Alhazzani W, Antonelli M, Coopersmith CM, French C, Machado FR, McIntyre L, Ostermann M, Prescott HC, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock 2021. Intensive Care Med. 2021;47(11):1181–247.
2. Stanski NL, Wong HR. Prognostic and predictive enrichment in sepsis. Nat Rev Nephrol. 2020;16(1):20–31.
3. Cazalis MA, Lepape A, Venet F, Frager F, Mougin B, Vallin H, Paye M, Pachot A, Monneret G. Early and dynamic changes in gene expression in septic shock patients: a genome-wide approach. Intensive Care Med Exp. 2014;2(1):20.
4. Namas RA, Vodovotz Y. From static to dynamic: a sepsis-specific dynamic model from clinical criteria in polytrauma patients. Ann Transl Med. 2016;4(24):492.
5. Wong HR, Cvijanovich NZ, Anas N, Allen GL, Thomas NJ, Bigham MT, Weiss SL, Fitzgerald JC, Checchia PA, Meyer K, et al. Endotype transitions during the acute phase of pediatric septic shock reflect changing risk and treatment response. Crit Care Med. 2018;46(3):e242–9.

6. Sweeney TE, Shidham A, Wong HR, Khatri P. A comprehensive time-course-based multicohort analysis of sepsis and sterile inflammation reveals a robust diagnostic gene set. Sci Transl Med. 2015. https://doi.org/10.1126/scitranslmed.aaa5993.
7. Bhavani SV, Semler M, Qian ET, Verhoef PA, Robichaux C, Churpek MM, Coopersmith CM. Development and validation of novel sepsis subphenotypes using trajectories of vital signs. Intensive Care Med. 2022;48(11):1582–92.
8. Bhavani SV, Wolfe KS, Hrusch CL, Greenberg JA, Krishack PA, Lin J, Lecompte-Osorio P, Carey KA, Kress JP, Coopersmith CM, et al. Temperature trajectory subphenotypes correlate with immune responses in patients with sepsis. Crit Care Med. 2020;48(11):1645–53.
9. Bhavani SV, Carey KA, Gilbert ER, Afshar M, Verhoef PA, Churpek MM. Identifying novel sepsis subphenotypes using temperature trajectories. Am J Respir Crit Care Med. 2019;200(3):327–35.
10. You SH, Kweon OJ, Jung SY, Baek MS, Kim WY. Patterns of inflammatory immune responses in patients with septic shock receiving vitamin C, hydrocortisone, and thiamine: clustering analysis in Korea. Acute Critical Care. 2023;38(3):286–97.
11. Annane D. The role of ACTH and corticosteroids for sepsis and septic shock: an update. Front Endocrinol (Lausanne). 2016;7:70.
12. Annane D, Pastores SM, Arlt W, Balk RA, Beishuizen A, Briegel J, Carcillo J, Christ-Crain M, Cooper MS, Marik PE, et al. Critical illness-related corticosteroid insufficiency (CIRCI): a narrative review from a multispecialty task force of the society of critical care medicine (SCCM) and the European society of intensive care medicine (ESICM). Intensive Care Med. 2017;43(12):1781–92.
13. Turnbull AV, Rivier CL. Regulation of the hypothalamic-pituitary-adrenal axis by cytokines: actions and mechanisms of action. Physiol Rev. 1999;79(1):1–71.
14. Cooper MS, Stewart PM. Corticosteroid insufficiency in acutely ill patients. N Engl J Med. 2003;348(8):727–34.
15. Wasyluk W, Wasyluk M, Zwolak A. Sepsis as a pan-endocrine illness—endocrine disorders in septic patients. J Clin Med. 2021;10(10):2075.
16. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, Bellomo R, Bernard GR, Chiche JD, Coopersmith CM, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801–10.
17. Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med. 1985;13(10):818–29.
18. Vincent JL, Moreno R, Takala J, Willatts S, De Mendonca A, Bruining H, Reinhart CK, Suter PM, Thijs LG. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996;22(7):707–10.
19. Chen HY, Elmer J, Zafar SF, Ghanta M, Moura Junior V, Rosenthal ES, Gilmore EJ, Hirsch LJ, Zaveri HP, Sheth KN, et al. Combining transcranial doppler and EEG data to predict delayed cerebral ischemia after subarachnoid hemorrhage. Neurology. 2022;98(5):e459–69.
20. Bhavani SV, Xiong L, Pius A, Semler M, Qian ET, Verhoef PA, Robichaux C, Coopersmith CM, Churpek MM. Comparison of time series clustering methods for identifying novel subphenotypes of patients with infection. J Am Med Inform Assoc. 2023;30(6):1158–66.
21. Eriksson J, Nelson D, Holst A, Hellgren E, Friman O, Oldner A. Temporal patterns of organ dysfunction after severe trauma. Crit Care. 2021;25(1):165.
22. Widmer IE, Puder JJ, Konig C, Pargger H, Zerkowski HR, Girard J, Muller B. Cortisol response in relation to the severity of stress and illness. J Clin Endocrinol Metab. 2005;90(8):4579–86.
23. Jenniskens M, Langouche L, Vanwijngaerden YM, Mesotten D, Van den Berghe G. Cholestatic liver (dys)function during sepsis and other critical illnesses. Intensive Care Med. 2016;42(1):16–27.
24. Fowler C, Raoof N, Pastores SM. Sepsis and adrenal insufficiency. J Intensive Care Med. 2023;38(11):987–96.
25. Yehya N, Fitzgerald JC, Hayes K, Zhang D, Bush J, Koterba N, Chen F, Tuluc F, Teachey DT, Balamuth F, et al. Temperature trajectory sub-phenotypes and the immuno-inflammatory response in pediatric sepsis. Shock. 2022;57(5):645–51.
26. Schenck EJ, Ma KC, Price DR, Nicholson T, Oromendia C, Gentzler ER, Sanchez E, Baron RM, Fredenburgh LE, Huh JW, et al. Circulating cell death biomarker TRAIL is associated with increased organ dysfunction in sepsis. JCI Insight. 2019. https://doi.org/10.1172/jci.insight.127143.
27. Linkermann A. Death and fire-the concept of necroinflammation. Cell Death Differ. 2019;26(1):1–3.
28. Cao C, Yu M, Chai Y. Pathological alteration and therapeutic implications of sepsis-induced immune cell apoptosis. Cell Death Dis. 2019;10(10):782.
29. Mira JC, Gentile LF, Mathias BJ, Efron PA, Brakenridge SC, Mohr AM, Moore FA, Moldawer LL. Sepsis pathophysiology, chronic critical illness, and persistent inflammation-immunosuppression and catabolism syndrome. Crit Care Med. 2017;45(2):253–62.
30. Evavold CL, Kagan JC. Inflammasomes: threat-assessment organelles of the innate immune system. Immunity. 2019;51(4):609–24.
31. Xiong S, Hong Z, Huang LS, Tsukasaki Y, Nepal S, Di A, Zhong M, Wu W, Ye Z, Gao X, et al. IL-1beta suppression of VE-cadherin transcription underlies sepsis-induced inflammatory lung injury. J Clin Invest. 2020;130(7):3684–98.
32. Engstrom L, Rosen K, Angel A, Fyrberg A, Mackerlova L, Konsman JP, Engblom D, Blomqvist A. Systemic immune challenge activates an intrinsically regulated local inflammatory circuit in the adrenal gland. Endocrinology. 2008;149(4):1436–50.
33. Kanczkowski W, Sue M, Zacharowski K, Reincke M, Bornstein SR. The role of adrenal gland microenvironment in the HPA axis function and dysfunction during sepsis. Mol Cell Endocrinol. 2015;408:241–8.
34. Xu Z, Mao C, Su C, Zhang H, Siempos I, Torres LK, Pan D, Luo Y, Schenck EJ, Wang F. Sepsis subphenotyping based on organ dysfunction trajectory. Crit Care. 2022;26(1):197.
35. Rivas M, Motes A, Ismail A, Yang S, Sotello D, Arevalo M, Vutthikraivit W, Suchartlikitwong S, Carrasco C, Iwuji K, et al. Characteristics and outcomes of patients with sepsis who had cortisol level measurements or received hydrocortisone during their intensive care unit management: a retrospective single center study. SAGE Open Med. 2023;11:20503121221146908.
36. Sam S, Corbridge TC, Mokhlesi B, Comellas AP, Molitch ME. Cortisol levels and mortality in severe sepsis. Clin Endocrinol (Oxf). 2004;60(1):29–35.
37. De Castro R, Ruiz D, Lavin BA, Lamsfus JA, Vazquez L, Montalban C, Marcano G, Sarabia R, Paz-Zulueta M, Blanco C, et al. Cortisol and adrenal androgens as independent predictors of mortality in septic patients. PLoS ONE. 2019;14(4): e0214312.
38. Bauer M, Gerlach H, Vogelmann T, Preissing F, Stiefel J, Adam D. Mortality in sepsis and septic shock in Europe, North America and Australia between 2009 and 2019—results from a systematic review and meta-analysis. Crit Care. 2020;24(1):239.
39. Liu B, Chen YX, Yin Q, Zhao YZ, Li CS. Diagnostic value and prognostic evaluation of Presepsin for sepsis in an emergency department. Crit Care. 2013;17(5):R244.
40. Egi M, Ogura H, Yatabe T, Atagi K, Inoue S, Iba T, Kakihana Y, Kawasaki T, Kushimoto S, Kuroda Y, et al. The Japanese clinical practice guidelines for management of sepsis and septic shock 2020 (J-SSCG 2020). J Intensive Care. 2021;9(1):53.
41. Rello J, van Engelen TSR, Alp E, Calandra T, Cattoir V, Kern WV, Netea MG, Nseir S, Opal SM, van de Veerdonk FL, et al. Towards precision medicine in sepsis: a position paper from the European Society of Clinical Microbiology and Infectious Diseases. Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis. 2018;24(12):1264–72.
42. Yu C, Yanfen C, Ying D, Bangjiang F, Minghua L, Zhongqiu L, Yiming L, Shinan N, Chuanyun Q, Yingping T, China sepsis/septic shock emergency treatment guidelines. J Clin Emerg Treat 2018.
43. Lin HY, Hsiao FY, Huang ST, Chen YC, Lin SW, Chen LK. Longitudinal impact of distinct infection trajectories on all-cause mortality of older people in Taiwan: a retrospective, nationwide, population-based study. Lancet Healthy longev. 2023;4(9):e508–16.

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