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Original Article

Factors predictive of serum cortisol in pediatric patients with acute physiological stress: a cohort study

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Highlights

- We identified predictors of cortisol in children under physiological stress.
- Age, sampling time, and vital signs were key predictive factors.
- Our findings may aid adrenal assessment and steroid replacement therapy.

Abstract. Measuring cortisol is crucial for assessing adrenal function in patients under stress; however, its value can fluctuate owing to various clinical factors. This study aimed to identify predictors of cortisol levels in pediatric patients with acute physiological stress. Children who were urgently admitted to the general ward or pediatric intensive care unit for acute illness or postoperative care were enrolled, while those with suspected adrenal function abnormalities or on current steroid therapy were excluded. Cortisol was measured in serum samples collected within 72 h of registration and its association with clinical factors was explored. A total of 397 samples from 217 patients were analyzed between August and November 2021 showing a median cortisol level of 375 nmol/L (interquartile range: 190–646 nmol/L). Multiple regression analysis with a mixed-effects model identified the following predictors of higher cortisol levels: heart rate z-score (+43.8 nmol/L/point), body temperature (+42.3 nmol/L/°C), Pediatric Early Warning System score (+44.3 nmol/L/point), age 3-6 yr (+68.8 nmol/L vs. < 1 yr), elapsed time < 4 h (+130.9 nmol/L vs. 4–12 h), and sampling time 6–10 AM (+96.4 nmol/L vs. 10 AM–2 PM). These variables independently predicted cortisol levels in pediatric patients during acute physiological stress.

Key words: cortisol, acute disease, adrenal insufficiency, stress response

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Introduction

Adrenocorticosteroids support cardiovascular circadian rhythm, with levels peaking in the morning (1–3). Stress enhances cortisol secretion via the limbic system, hypothalamus, and pituitary gland (1), thereby supporting cardiovascular and neurological function, fluid balance, immunity, and metabolism (4). In patients with adrenal insufficiency, exposure to physical stress without adequate steroid supplementation can lead to the breakdown of homeostasis and potential death (5).

Evaluating adrenal function during stress is a crucial but challenging task. Stimulation tests are the gold standard (6–8), but are often infeasible in urgent situations. Random blood sampling can help determine the need for steroid supplementation (9, 10). It is important to note that adrenocorticosteroid secretion can be influenced by various factors and is known to increase to especially high levels during major surgery or severe acute illness (10–12).

Understanding the factors affecting adrenocorticosteroid secretion during stress is also vital for evaluating the need for steroid supplementation in patients with adrenal insufficiency. Guidelines exist for managing stress in patients with primary adrenal insufficiency (7, 13); however, evidence on dosing is limited, partly because of the difficulty of conducting randomized trials. Extrapolating results from other populations is therefore essential for establishing a dosing protocol. For example, an effective approach may involve the combination of findings from pharmacokinetic studies on changes in blood steroid levels after administration (14) and steroid activity in patients with adrenal insufficiency (15), as well as physiological research on steroid secretion patterns under stressful conditions in otherwise healthy individuals (12).

Despite the importance of understanding the patterns of adrenocorticosteroid secretion in acute disease states, pediatric data are scarce. The present study aimed to identify predictors of cortisol levels in pediatric patients with acute physiological stress, including acute-onset illnesses and early postoperative states, and to propose age-appropriate reference values for cortisol levels.

Methods

Study design and setting

This single-center prospective observational study was conducted in the emergency department (ED), general ward, and pediatric intensive care unit (PICU) of a tertiary pediatric hospital in Tokyo between August and November 2021. It was approved on June 16, 2021 by the Institutional Review Board of the study center (approval code: 2021b-6). Participants were provided with an opt-out clause on the institutional website.

Participants

The inclusion criteria comprised: (i) urgent admission to the general ward due to an acute illness (e.g., sepsis or trauma) or PICU admission for intensive/perioperative care, and (ii) age of 1 wk to less than 20 yr. The exclusion criteria were as follows: (i) an underlying condition affecting adrenal function; (ii) previous systemic steroid use; (iii) suspected adrenal dysfunction due to acute illness; (iv) refusal to participate; and (v) any case judged by the investigator as potentially compromising the quality of the study data or generalizability of the results. Sedative use in the PICU was not an exclusion criterion.

Data source and variables

Cortisol level was measured using residual serum collected within 72 h of registration. Most samples obtained from the ED and general wards were collected via venipuncture without anesthesia, while most collected in the PICU were obtained via arterial lines. The samples were frozen, and after enrollment in the entire cohort, a batch was sent to SRL, Inc. (Tokyo, Japan) for electrochemiluminescence immunoassay (ECLIA). The concentrations were expressed in μg/dL and were then multiplied by 27.59 to convert to nmol/L. Measurements were reported only to the researchers. If a patient presented with unexplained hypoglycemia, significant lethargy, shock, or treatment-resistant hyponatremia, the attending physicians independently ordered cortisol measurements to rule out adrenal insufficiency, separate from the study protocol.

Clinical data were extracted from the electronic medical records. Registration time was defined as the triage time for ED admission or transfer from the general ward to the PICU. The patient parameters included age, sex, underlying disease(s), and acute conditions. Elapsed time was defined as the duration from registration to blood collection. The parameters for each sample included sampling time, patient vital signs, Pediatric Early Warning System (PEWS) score, and treatment conditions (triage color in the ED (16); intubation or vasopressor use in the PICU). The PEWS score is designed to predict clinical deterioration by evaluating the severity of circulatory, respiratory, and behavioral disturbances. Each scale ranges from 0 to 3, and the overall assessment is obtained by summing the individual scores (17).

Statistical analysis

Cortisol level was treated as a dependent variable, and its association with independent variables was analyzed using bivariate analysis with the Wilcoxon rank-sum test for binary variables and the Kruskal–Wallis test for other categorical variables. The z-scores for heart rate and respiratory rate were calculated using previously reported reference values (18). Briefly, the

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median for each age group was assumed to be equal to the mean. The standard deviation was estimated by multiplying the difference between the 90th percentile and the median by 0.8. Spearman's rank correlation coefficient was used for quantitative variables. Multivariate analysis was performed using a mixed-effects regression model with patient ID as a random effect. Sensitivity analysis was stratified according to treatment disposition and elapsed time. This exploratory study aimed to generate hypotheses based on data from 100 patients in a general ward and 100 patients in the PICU. The P values were used as references. All analyses were performed using R ver. 4.3.3, developed by the R Core Team and maintained by the Comprehensive R Archive Network (CRAN).

Results

Patients transferred from the ED to the general ward, and those transferred from the ED or general ward to the PICU were screened. In total, 217 participants were enrolled in this study (**Fig. 1**). Over half of the exclusions were due to the previous use of a systemic steroid, mainly dexamethasone for asthma or methylprednisolone for cardiac surgery. Cortisol levels were measured in 397 samples. Samples were available for 94.1% of the patients eligible for PICU admission (112/119), but only 46.1% of those eligible for general ward admission (105/228). On an average, 2.46 samples per PICU patient and 1.16 samples per general ward patient were analyzed.

The baseline characteristics included a median age of 35 mo (interquartile range [IQR]: 10-84), with no significant differences between the groups in terms of age or sex (**Table 1**). Infections and postoperative follow-up accounted for 23.5% of the acute conditions, followed by seizures (8.8%) and trauma (6.9%). Differences between the groups included no postoperative cases in the general ward and no urinary tract infections or Kawasaki disease in the PICU. Underlying diseases were present in 59.0% of patients and were more prevalent in PICU patients, especially those with neurological disorders (46.4%). No adrenal crisis or death occurred during hospitalization.

The median cortisol level was 375 nmol/L (IQR: 190–646). Supplementary Figure 1 shows the changes in cortisol values over time in all patients. **Figure 2** shows the factors correlating with cortisol levels, including elapsed time ($R = -0.41$), heart rate ($R = 0.45$), respiratory rate ($R = 0.31$), body temperature ($R = 0.38$), and PEWS score ($R = 0.21$). There was no significant correlation with SpO_2. **Table 2** shows the association between cortisol level and clinical factors. A higher median cortisol value was associated with age 3–6 yr (444 nmol/L), acute infection (497 nmol/L), elapsed time < 4 h (601 nmol/L), early morning (6–10 AM, 468 nmol/L), and blue or red triage in the ED (668 nmol/L).

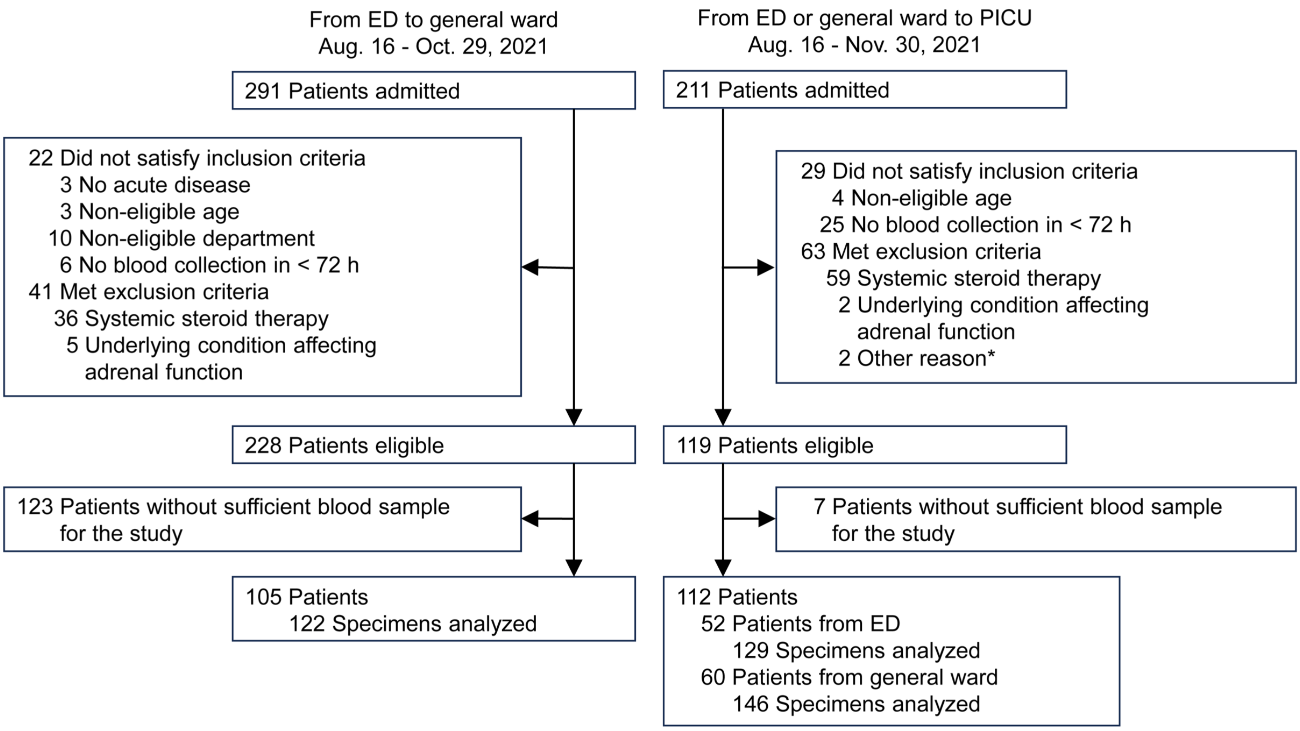

Fig. 1. Patient flow diagram. Diagram illustrating the selection and categorization of 502 screened pediatric patients. A total of 217 patients were included and 397 specimens were analyzed. ED, emergency department; PICU, pediatric intensive care unit. * Two patients were excluded for the following reasons. Access to the electronic medical records of one patient was restricted by the administrator because he was under suspicion of child abuse. The second patient was transferred to the general ward after 27 d in the PICU, where she was readmitted on the day following her transfer for ventilator adjustment, despite being clinically stable.

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Table 1. Baseline characteristics of the patients

	From ED to general ward		From ED or general ward to PICU	
	n	(%)	n	(%)
Overall	105		112	
Sex, male	56	(53.3)	63	(56.3)
Age in yr				
< 1	23	(21.9)	31	(27.7)
≥ 1, < 3	36	(34.3)	18	(16.1)
≥ 3, < 6	21	(20.0)	27	(24.1)
≥ 6, < 12	17	(16.2)	23	(20.5)
≥ 12	8	(7.6)	13	(11.6)
Acute condition *				
Postoperative follow-up				
Neurological	0	(0.0)	19	(17.0)
Gastrointestinal	0	(0.0)	12	(10.7)
Other surgery	0	(0.0)	16	(14.3)
Infection				
Respiratory tract	14	(13.3)	15	(13.4)
Urinary tract	9	(8.6)	0	(0.0)
Other infection	11	(10.5)	2	(1.8)
Seizure	12	(11.4)	7	(6.3)
Trauma	4	(3.8)	11	(9.8)
Others				
Kawasaki disease	14	(13.3)	0	(0.0)
Asthma	11	(10.5)	2	(1.8)
Other diseases	30	(28.6)	28	(25.0)
Underlying condition (s) *				
No (otherwise healthy)	56	(53.3)	31	(27.7)
Neurological	12	(11.4)	52	(46.4)
Cardiac	15	(14.3)	23	(20.5)
Gastrointestinal	10	(9.5)	28	(25.0)
Congenital malformation	11	(10.5)	17	(15.2)
Others	34	(32.4)	40	(35.7)

* Each patient had only one acute condition but may have had more than one underlying condition. ED, emergency department; PICU, pediatric intensive care unit.

Supplementary Table 1 shows the results of a post-hoc analysis detailing where differences occurred among the subcategories of each categorical variable. Multiple regression analysis did not detect an association between cortisol level and respiratory rate, acute condition, or medical situation, but did find associations with heart rate, body temperature, PEWS score, age, elapsed time, and sampling time (**Table 3**). There was no significant multicollinearity among the variables (Supplementary Tables 2 and 3). The model's intercept of 574.4 nmol/L represented the estimated cortisol level at the reference values of body temperature 37.0°C, average heart rate and respiratory rate, PEWS score = 0, age < 1 yr, postoperative follow-up, elapsed time < 4 h, sampling time 6–10 AM, and general ward admission. A high cortisol level was associated with increased body temperature (+42.3 nmol/L/°C), heart rate z-score (+43.8 nmol/L/point), PEWS score (+44.3 nmol/L/point), age 3–6 yr (+68.8 nmol/L vs. < 1 yr), elapsed time < 4 h (+130.9 nmol/L vs. 4–12 h), and sampling time 6–10 AM (+96.4 nmol/L vs. 10 AM–2 PM). These associations were generally observed in a subgroup analysis of PICU vs. general ward patients and for samples collected < 4 h vs. > 4 h after registration (Supplementary Tables 4–11, Supplementary Figs. 2–5).

Discussion

Bivariate analysis revealed that cortisol level was associated with elapsed time, heart rate, respiratory rate, body temperature, PEWS score, age, acute condition, sampling time, and medical situation. Among these, heart rate, body temperature, PEWS score, age, elapsed time, and sampling time were also associated with cortisol level in the multiple regression analysis.

The associations between cortisol level and heart rate, body temperature, and PEWS score can be explained by the effect of stressors such as psychological (19), respiratory, and circulatory disturbances, which influence both cortisol secretion and variations in vital signs (1, 4, 20). Although direct studies on the association between children's cortisol levels and vital signs or PEWS

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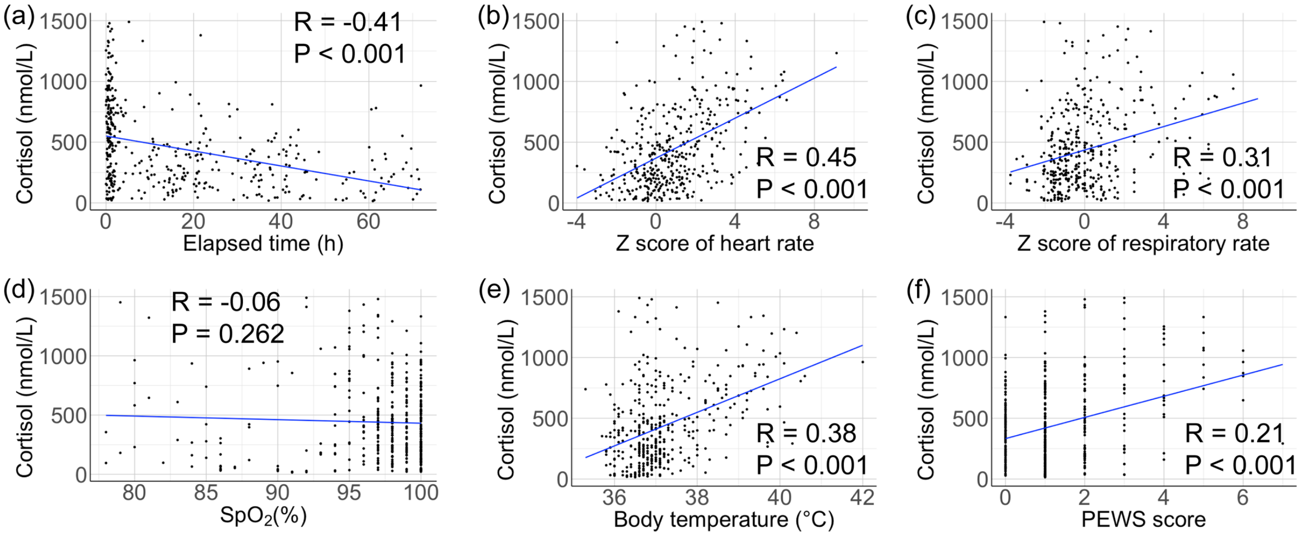

Fig. 2. Scatter plots of cortisol level vs. clinical parameters. The scatter plots show the relationship between cortisol level and various clinical parameters, with each plot highlighting a different variable: (a) elapsed time (h) from registration, (b) z score of heart rate, (c) z score of respiratory rate, (d) percutaneous oxygen saturation (SpO_2), (e) body temperature, and (f) Pediatric Early Warning System (PEWS) score. The R and P values represent the results of the Spearman correlation analysis between the variables on the x-axis and the cortisol value on the y-axis. The blue line indicates linear regression.

scores are scarce, the findings of studies linking cortisol value to outpatient heart rate (21) and the severity of acute respiratory distress syndrome (20) are consistent with those of the present study. The cortisol response varies by age, with one study showing that response to corticotropin-releasing hormone is negatively associated with age (22) and another demonstrating a positive correlation (23), underscoring the difficulty in generalizing the age-related mechanisms involved. The fact that cortisol peaked between 6–10 AM suggests that the circadian rhythm is maintained even under stress, as supported by previous research (24).

Multiple regression analysis did not reveal any significant differences in acute conditions or medical situations, in contrast with previous studies (11, 12). Bivariate analysis demonstrated an association with these factors; however, multivariate analysis suggested that sampling time and vital sign assessments were sufficient to estimate the cortisol level, implying that these were adequate predictors. These findings provide important insights into the evaluation and treatment of adrenal insufficiency, and can promote further discussion. For example, a cortisol level < 276 nmol/L on random blood sampling, as observed in patients with tachycardia or a high PEWS score at the start of treatment, meets the criteria for critical illness-related corticosteroid insufficiency (25). In contrast, for patients with adrenal insufficiency and acute physiological stress but mild vital sign abnormalities, a lower steroid dosage may be considered for stress management.

The persistent association with elapsed time, even after adjustments, is likely to result from the resolution of stress-inducing factors such as inflammation or trauma. The significant reduction in cortisol levels observed during the first 24 h may support the validity of a treatment strategy that mimics normal cortisol production by tapering steroid supplementation for 2–3 d (26). However, the validation of stress management protocols requires additional evidence. For instance, in a previous study, after a bolus of hydrocortisone 50 mg was administered to dexamethasone-suppressed, adult patients, the mean (± standard error) plasma cortisol value peaked at 2450 (±360) nmol/L at 30 min, then decreased to approximately 600 nmol/L at 5 h (27). This peak level was substantially higher than the value at 0–4 h after registration in the present study. Nevertheless, it remains unclear whether the cortisol levels observed in the previous study were maintained beyond 6 h at the levels observed in the present study. However, another study involving continuous infusion of hydrocortisone 200 mg over 24 h in adult patients with primary adrenal insufficiency reported median minimum and maximum serum cortisol levels of 520 and 836 nmol/L, respectively (14). The adjusted mean cortisol levels in the first 4 h of our study fell between these median values, but decreased below them afterward. Excess cortisol can cause hyperglycemia and hypertension, whereas cortisol deficiency can cause adrenal insufficiency. Therefore, aiming for a concentration closer to the endogenous level, for example by combining a bolus with a continuous infusion, may be ideal. In the challenging realm of stress management for which randomized studies are difficult to perform, the accumulation and extrapolation of various types of evidence are crucial.

The limitations of the present study include a potential selection bias, particularly in the ED-to-

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Table 2. Association between cortisol level and categorical variables

	n	Cortisol (nmol/L)			P value
		1st quartile	Median	3rd quartile	
Overall	397	189	375	646	
Sex					0.12
Male	209	199	389	654	
Female	188	164	346	612	
Age in yr					< 0.001
< 1	111	110	263	481	
≥ 1, < 3	92	212	422	740	
≥ 3, < 6	84	251	444	807	
≥ 6, < 12	66	180	332	545	
≥ 12	44	188	370	539	
Acute condition					< 0.001
Postoperative follow-up	113	148	290	458	
Infection	82	246	497	816	
Seizure	36	224	410	849	
Trauma	28	148	323	487	
Others	138	181	390	641	
Underlying condition(s)					0.063
No (otherwise healthy)	140	211	415	726	
Yes (if any)	257	177	348	596	
Elapsed time from registration (h) *					< 0.001
< 4	174	273	601	847	
≥ 4, < 12	33	233	345	458	
≥ 12, < 24	76	164	263	447	
≥ 24, < 48	74	129	275	403	
≥ 48, < 72	40	94	200	336	
Sampling time					0.001
≥ 6 AM, < 10 AM	44	204	468	915	
≥ 10 AM, < 2 PM	98	223	393	700	
≥ 2 PM, < 6 PM	60	210	461	753	
≥ 6 PM, < 10 PM	50	157	407	744	
≥ 10 PM, < 2 AM	33	244	397	648	
≥ 2 AM, < 6 AM	112	135	265	441	
Medical situation					< 0.001
ED, yellow or green in triage	62	248	557	723	
ED, blue or red in triage	85	292	668	941	
General ward	25	211	331	469	
PICU, no intubation	91	198	361	481	
PICU, intubation	86	175	276	495	
PICU, intubation and vasopressor	48	51	160	270	

* Registration time was defined as the time of triage in patients admitted directly from the ED to the general ward or PICU, and the time of admission in patients admitted from the general ward to the PICU. ED, emergency department; PICU, pediatric intensive care unit.

general ward group, owing to the small number of cortisol measurements. Undiagnosed critical illness-related corticosteroid insufficiency cannot be ruled out. Additionally, this was a single-center study; thus, its findings may have limited generalizability. Adjustment for potential confounders in the multivariate analysis may have been inadequate owing to the lack of clarity about causality and the risk of repeated testing producing spurious differences. Furthermore, all samples from patients transferred from the ED to the general ward and most samples collected within 4 h from patients transferred from the ED to the PICU were obtained via venipuncture. Theoretically, the cortisol levels in these patients may have increased in response to pain caused by the procedure, potentially introducing bias into the results.

Conclusions

Multivariate analysis revealed that independent

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Table 3. Results of the multiple regression analysis with cortisol value (nmol/L) as the outcome variable

	Estimate (coefficient)	Standard error	P value
Intercept *	574.4	93.1	< 0.001
Z score of heart rate †	43.8	10.1	< 0.001
Z score of respiratory rate †	–6.08	9.00	0.499
Body temperature –37.0 (°C) *	42.3	18.4	0.022
PEWS	44.3	14.5	0.002
Age in yr			
< 1	Reference		
≥ 1, < 3	68.8	52.7	0.194
≥ 3, < 6	163.0	55.2	0.004
≥ 6, < 12	88.8	57.5	0.124
≥ 12	–29.2	68.0	0.668
Acute condition			
Postoperative follow-up	Reference		
Infection	65.7	53.4	0.219
Seizure	–34.8	71.4	0.627
Trauma	12.1	76.2	0.874
Other	11.2	48.5	0.818
Elapsed time from registration (h) ‡			
< 4	Reference		
≥ 4, < 12	–130.9	62.6	0.038
≥ 12, < 24	–240.5	57.8	< 0.001
≥ 24, < 48	–257.3	58.5	< 0.001
≥ 48, < 72	–278.3	67.0	< 0.001
Sampling time *			
≥ 6 AM, < 10 AM	Reference		
≥ 10 AM, < 2 PM	–96.4	46.6	0.039
≥ 2 PM, < 6 PM	–167.2	53.0	0.002
≥ 6 PM, < 10 PM	–218.5	55.3	< 0.001
≥ 10 PM, < 2 AM	–205.5	62.0	0.001
≥ 2 AM, < 6 AM	–97.9	48.1	0.043
Medical situation			
General ward	Reference		
ED, yellow or green in triage	–111.2	78.9	0.160
ED, blue or red in triage	–136.7	84.0	0.105
PICU, no intubation	13.4	65.6	0.838
PICU, intubation	–42.5	69.8	0.543
PICU, intubation and vasopressor	–83.2	81.1	0.305

* The intercept is the estimated cortisol concentration when all categorical variables are the same as the reference and all quantitative variables are zero. To make the results intuitive and understandable, the body temperature minus 37.0, which is close to the normal temperature, was used as the independent variable, and the reference for the sampling time was the time of day, commonly used to assess the basal cortisol level. † The z-score of the heart rate and respiratory rate was calculated based on the study by Fleming *et al*. (2011), where the median for each age group was estimated as the mean, and the 90th percentile minus the median multiplied by 0.8 was approximated as the standard deviation. ‡ Registration time was defined as the time of triage in patients transferred directly from the ED to the general ward or the PICU and the time of admission in patients transferred from the general ward to the PICU. ED, emergency department; PEWS, Pediatric Early Warning Score; PICU, pediatric intensive care unit.

predictors of cortisol value in pediatric patients with acute physiological stress were neither the acute condition itself nor the medical situation, but rather heart rate, body temperature, PEWS score, age, elapsed time from registration, and sampling time. These findings provide important insights for the diagnosis and treatment of adrenal insufficiency.

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Data availability statement: All the data generated or analyzed during this study are included in this article and its supplementary material files. Further enquiries can be directed to the corresponding author.

Conflict of interests: Yukihiro Hasegawa received a lecture fee of 5 million JPY from Novo Nordisk Pharma in 2023. None of the other authors have any conflicts of interest to declare.

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