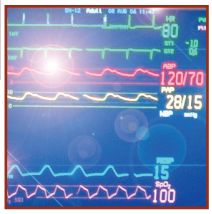

Temperature Profile and Adverse Outcomes After Discharge From the Intensive Care Unit

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Background A predictive model that uses the rhythmicity of core body temperature (CBT) could be an easily accessible clinical tool to ultimately improve outcomes among critically ill patients.

Objectives To assess the relation between the 24-hour CBT profile (CBT-24) before intensive care unit (ICU) discharge and clinical events in the step-down unit within 7 days of ICU discharge.

Methods This retrospective cohort study in a tertiary ICU at a single center included adult patients requiring acute invasive ventilation for more than 48 hours and assessed major clinical adverse events (MCAEs) and rapid response system activations (RRSAs) within 7 days of ICU discharge (MCAE-7 and RRSA-7, respectively).

Results The 291 enrolled patients had a median mechanical ventilation duration of 139 hours (IQR, 50-862 hours) and at admission had a median Acute Physiology and Chronic Health Evaluation II score of 22 (IQR, 7-42). At least 1 MCAE or RRSA occurred in 64% and 22% of patients, respectively. Independent predictors of an MCAE-7 were absence of CBT-24 rhythmicity (odds ratio, 1.78 [95% CI, 1.07-2.98]; $P=.03$), Sequential Organ Failure Assessment score at ICU discharge (1.10 [1.00-1.21]; $P=.05$), male sex (1.72 [1.04-2.86]; $P=.04$), age (1.02 [1.00-1.04]; $P=.02$), and Charlson Comorbidity Index (0.87 [0.76-0.99]; $P=.03$). Age (1.03 [1.01-1.05]; $P=.006$), sepsis at ICU admission (2.02 [1.13-3.63]; $P=.02$), and Charlson Comorbidity Index (1.18 [1.02-1.36]; $P=.02$) were independent predictors of an RRSA-7.

Conclusions Use of CBT-24 rhythmicity can assist in stratifying a patient's risk of subsequent deterioration during general care within 7 days of ICU discharge. (*American Journal of Critical Care.* 2022;31:e1-e9)

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Organ system physiology and behaviors—for example, body temperature, brain wave activity, cardiac and respiratory function, blood coagulation, immune function, and drug metabolism—often follow rhythmic circadian patterns.[1,2] Disturbances in the timing of biological processes, or circadian rhythm disruption (CRD), are common in critically ill patients,[3] and various factors contribute, such as ambient light and noise, acute and chronic disease, sleep disruption, and the timing of therapy regimens.[3-8] Core body temperature (CBT) is a reliable and stable indicator of circadian timing in health,[9] and it is a routine clinical measure for determining whole-body homeostasis or characterizing hypothermia or fever.[10]

Patients commonly deteriorate clinically after discharge from an intensive care unit (ICU)[11]; this deterioration results in ICU readmissions,[12-14] higher mortality,[12,15] prolonged hospital stay,[16] and higher overall health care costs.[17] The presence of CRD may mark the persistence or development of a disease process, putting the patient at risk for clinical deterioration or a new clinical event. The proportion of patients who have CRD at ICU discharge and the relation between CRD and adverse effects during general care after an ICU stay are not known. The Temperature Profile and Adverse Outcomes Post ICU Discharge (TAOPID) study aimed to assess CBT profile during the 24 hours of ICU admission before discharge (CBT-24) as a predictor for rapid response system activation (RRSA) or a major clinical adverse event (MCAE) within 7 days after ICU discharge.

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Methods

We assembled a retrospective cohort study that included sequential adult patients who were discharged to a step-down unit after an acute admission to an ICU between 2015 and 2016. All included patients required mechanical ventilation for longer than 48 hours. We excluded from the cohort patients who were febrile at the time of ICU discharge or who were discharged with clear limitations on escalating care in the event of clinical deterioration; this group excluded patients who were discharged to palliative care. Patients recovering from acute brain injury or neurological injury were also excluded because of a significant risk of structural injury to their circadian pacemaker. Patients with a burn injury were excluded because they often have abnormal thermoregulation. Patients who met the inclusion criteria were sourced from the Royal Brisbane and Women's Hospital MetaVision database (iMDsoft). This data set is well established and has been validated; it is used to collect real-time local data for inclusion in a national performance survey of critically ill patients through the Australia and New Zealand Intensive Care Centre for Outcome and Resource Evaluation. For patients with multiple ICU admissions within the study period, we included data from only the first ICU admission. The study received institutional ethical approval by the Research Ethics Committee of the Royal Brisbane and Women's Hospital (LNR/2018/QRBW/48281).

The principal study outcomes were the number of MCAEs assessed within 7 days of ICU discharge (MCAE-7) and the number of RRSAs assessed within 7 days of ICU discharge (RRSA-7), based on the concept of 7 days as a practical follow-up period after ICU discharge. We collected RRSA data from the Rapid Response System database of the Safety and Quality Unit of the Royal Brisbane and Women's Hospital. In addition to the time when the RRSA occurred, this database also records call criteria (cardiac arrest, threatened airway, breathing, circulation, neurology, worry) and the call outcome (death, palliative care, transfer

to coronary care unit, transfer to ICU, or remained in general care area).

We assessed clinical adverse events as a secondary outcome and defined them a priori; relevant data were collected retrospectively from electronic clinical charts in the integrated electronic medical record (Cerner) (see Supplemental Table 1).[18] An MCAE was defined as a combined end point of new-onset nosocomial pneumonia, confusion, or delirium; a deep venous thrombosis or pulmonary embolus; a myocardial infarction or new-onset arrhythmia; and a catheter-related bloodstream infection or a urinary tract infection. Conditions identified during chart review, such as delirium, were defined per clinicians' records; although such definitions potentially increase the generalizability of the findings, they may limit the findings' validity.

The principal independent variable was the final complete CBT-24, which represents temperature during the 24 hours before ICU discharge and was based on clinical temperatures recorded with an indwelling urinary catheter thermistor. Esophageal, tympanic, and axillary temperatures (in order of preference) were included only when bladder temperatures were not available. We assessed temperature profiles using the R statistical program and R package CircaCompare[19]; we compared patients' CBT-24 measurements with those from simulated sex-matched controls, which we obtained from publicly available data.[20] We analyzed CBT profiles for the presence of circadian rhythmicity ($P<.05$); if rhythmicity was present we assessed the amplitude, the mesor or the midpoint of the oscillation, and the phase ($P<.05$). Patients with a body temperature higher than 38.5 °C were considered to be febrile.

Additional clinical data to describe the cohort included the Charlson Comorbidity Index,[21] principal diagnosis at ICU admission (surgical, elective, medical, trauma, obstetric), hospital mortality, hospital and ICU lengths of stay, inotrope use, dialysis therapy, ileus, sepsis requiring antibiotic therapy at admission, and Acute Physiology and Chronic Health Evaluation (APACHE) II[22] and Sequential Organ Failure Assessment (SOFA)[23] scores both at ICU admission and upon discharge. We used APACHE II and SOFA scores at ICU discharge in an attempt to quantify the severity of illness at that time point, consistent with previous studies.[24,25] Medications administered within the 24 hours before ICU discharge were characterized by drug class; sedation on the day of discharge was summarized as a composite of major tranquilizers, narcotics, sedatives including α_2-agonists, and benzodiazepines.

Statistical Methods

We entered data into a purpose-built Microsoft Access research database (Microsoft Corp) and then analyzed the data using Stata 15 statistical software (StataCorp) to identify univariate associations and perform logistic regression modeling of the outcome of interest. After data linkage, the data used for the analysis were deidentified.

Sample size calculations were limited because no published data were avilable for the rate of circadian disruption or the frequency of RRSAs or MCAEs among patients at ICU discharge. We conservatively estimated the rate of RRSA or MCAE after ICU discharge to be 14%.[12] Based on results of the *z*-test for a single proportion, 58 patients would be required if the absence of circadian temperature rhythmicity increased the RRSA rate to 25%. We aimed to enroll 300 patients in this initial pilot study, and considering the rule of thumb of 10 individuals with either an MCAE or an RRSA for each explanatory variable, the regression modeling should be able to support approximately 5 explanatory variables in the final model.[26] For descriptive statistics, we calculated absolute and relative frequencies for categorical parameters and characterized continuous parameters using median and interquartile range (IQR), though we provide an actual range when we consider it to be clinically relevant. We used the *t*, χ^2, Fisher exact, and Wilcoxon rank sum tests for inferential statistics, as appropriate. Results were considered to be statistically significant when *P* was .05 or less. We constructed forward, stepwise logistic models for RRSA-7 and MCAE-7. We considered variables for inclusion in the model when associations had a *P* of .25 or less in the univariate analysis or were clinically relevant. Goodness of fit was assessed with the Hosmer-Lemeshow statistic, whereas calibration was assessed on the basis of the area under the receiver operating characteristic curve. Sensitivity/specificity plots were derived for the probability of RRSA-7 and MCAE-7 at the median values of the covariants in the respective regression models.

> The rhythmicity of core body temperature profiles was assessed in addition to severity of illness at time of ICU discharge.

Results

We enrolled 291 patients in the study. Table 1 summarizes their demographic information, including age, ICU and hospital lengths of stay, case mix, comorbid conditions, and APACHE II and SOFA

Table 1
Demographic characteristics of 291 patients in the study

Variable[a]	Value[a]
Age, y	57 (19-82), 18-90
Male sex	188 (64.6)
ICU length of stay, d	8 (2-43), 2-51
Hospital length of stay, d	26.7 (4.9-105.9), 3.7-137.1
Admission type	
Medical	212 (72.9)
Surgical	25 (8.6)
Trauma	54 (18.6)
Sepsis as part of ICU primary admission	119 (40.9)
Acute renal failure	40 (13.8)
Charlson Comorbidity Index	2 (0-8), 0-10
Comorbidities	
None	1 (0.3)
1	144 (49.5)
2	55 (18.9)
3	50 (17.2)
4	28 (9.6)
5	6 (2.1)
6	6 (2.1)
7	1 (0.3)
SOFA score	
ICU admission	11 (2-19), 0-20
ICU discharge	4 (0-12), 0-14
APACHE II score	
ICU admission	22 (7-42), 4-45
ICU discharge	13 (2-27), 0-40
APACHE III score at ICU admission	68 (25-148), 21-161
APACHE II chronic health categories (n=289 patients)	
Renal	8 (2.8)
Cardiovascular	3 (1.0)
Respiratory	6 (2.1)
Immunocompromised	12 (4.1)
Liver	13 (4.5)
Nonoperative or emergency postoperative patients.	289 (100.0)
Duration of invasive ventilation, h	139 (50-862), 49-1211
Duration of sedation, h	119 (11-566), 0-826
Duration of noninvasive ventilation, h (n=89)	7 (1-82), 1-137
Duration of continuous dialysis, h (n=60)	120.5 (27-369), 5-745
Duration of inotropic therapy, h (n=208)	49.5 (2-342), 1-541
Duration of Ileus, h (n=73)	118 (16-450), 2-875
Sedation and analgesia drug use 24 hours before discharge	
Antidepressants	25 (8.6)
Benzodiazepines	67 (23.0)
Major tranquilizers	52 (17.9)
Narcotic sedatives (including α_2-agonists)	132 (45.4)
α_2-Agonists	52 (17.9)
Patients' hospital outcomes	
Survived ICU, died in hospital	25 (8.6)
Died in ICU (upon readmission to ICU)	1 (0.3)
Transferred to chronic care or rehabilitation	75 (25.8)
Transferred to another acute care hospital	39 (13.4)
Discharged home	151 (51.9)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; IQR, interquartile range; SOFA, Sequential Organ Failure Assessment.

[a] Unless otherwise indicated, data are No. (%) of patients or median (IQR), range.

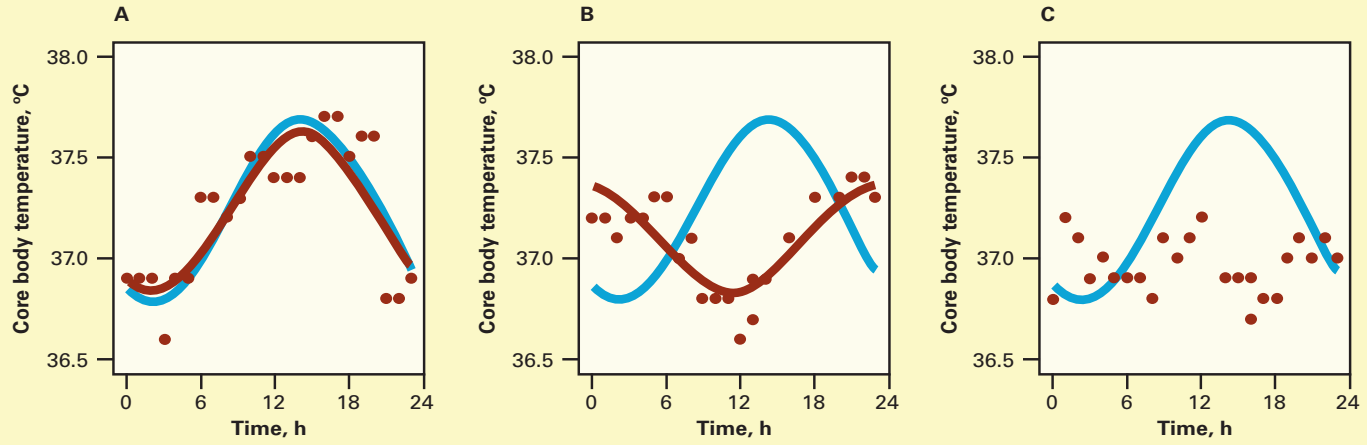

Figure Representative graphs comparing circadian profiles of intensive care patients' core body temperature with a normal temperature profile. A, Patient showing no significant difference in phase, amplitude, or mesor (midpoint of oscillation) from healthy controls. Rhythmicity difference, $P<.001$; mesor difference, $P=.99$; amplitude difference, $P=.45$; phase difference, $P=.69$. B, Patient showing a significant phase delay but no amplitude or mesor difference from healthy controls. Rhythmicity, $P<.001$; mesor difference, $P=.08$; amplitude difference, $P=.18$; phase difference, 9.13 ($P<.001$). C, Patient showing no rhythmic temperature profile. Rhythmicity, $P=.37$.

scores at admission and discharge. All patients received some form of active central nervous system analgesia or sedation within the 24 hours before ICU discharge. Of the 48 patients prescribed a sedative agent, only 8 (17%) received dexmedetomidine, whereas 30 (63%) received clonidine. Details about medication administration during the 24 hours before ICU discharge are summarized in Supplemental Table 2, and details about the Charlson comorbidities are summarized in Supplemental Table 3.

Data to analyze temperature profile were available from 289 patients. A median of 22 temperature measurements (IQR 11-24) were available for each of these patients. A minimum of 6 measures were required for cosinor analysis. In most patients, temperature had been measured at a range of sites; a breakdown of temperature measurement sources is detailed in Supplemental Table 4. Among these 289 patients, at ICU discharge, 191 (66%) had a temperature profile that was considered rhythmic by cosinor analysis ($P<.05$). The median mesor or central temperature of the oscillation was 37.4 °C (IQR 37.1-37.7), with a median amplitude of 0.28 °C (IQR 0.20-0.40) and median peak time of 4:25 PM (IQR 1:20 PM-7:13 PM). Temperature peaked between 9 PM and 6 AM in 43 patients (23%). Representative temperature profiles are detailed in the Figure.

After ICU discharge, 100 RRSAs occurred; 64 patients (22%) had at least 1 RRSA. Median APACHE II and SOFA scores, along with additional RRSA details, are shown in Table 2. A breathing disturbance was the most common reason for an RRSA (n = 73 [73.0%]), although some patients were delirious or required cardiopulmonary resuscitation. With regard to RRSA outcomes, in most cases patients either remained in the general care area or were readmitted to the ICU;

Table 2
Summary of characteristics of rapid response system activations among 291 study patients

Parameter	Value[a]
Total No. of RRSA events	100
Patients requiring at least 1 RRSA	64 (22.0)
No. of RRSA events per patient	
0	229 (78.7)
1	45 (15.5)
2	10 (3.4)
3	4 (1.4)
4	3 (1.0)
5	1 (0.3)
6	1 (0.3)
Time to RRSA following ICU discharge, d (n = 100 events)	4.5 (0-42), 0-57
RRSA within 7 days of ICU discharge	62 (62.0)
RRSA within 14 days of ICU discharge	80 (80.0)
APACHE II score at time of RRSA (n = 100 events)	15 (7-33), 6-40
SOFA score at time of RRSA (n = 100 events)	5 (0-11), 0-13
RRS-A event criteria	
Cardiac arrest	3 (3.0)
Threatened airway	6 (6.0)
Breathing difficulty	73 (73.0)
Neurologic disturbance	37 (37.0)
Pain	8 (8.0)
Sepsis	11 (11.0)
Delirium on day of RRSA	39 (39.0)
RRS-A event outcome	
Died within 24 hours of RRSA	3 (3.0)
Remained in general care area	82 (82.0)
Transferred to ICU	15 (15.0)
Palliation	
Commenced after RRSA event	7 (7.0)
Palliated already at time of RRSA event	3 (3.0)

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; IQR, interquartile range; RRS-A, rapid response team activation; SOFA, Sequential Organ Failure Assessment.

[a] Data are median (IQR), range or No. (%) among 100 events, unless otherwise indicated.

Table 3
Summary of clinical event characteristics for 291 patients in the study

Characteristic	Value
No. (%) of patients with clinical events	192 (66.0)
Total No. of clinical events	597
No. of clinical events per patient, No. (%) of 291 patients	
0	99 (34.0)
1	77 (26.5)
2	50 (17.2)
3	32 (11.0)
4	7 (2.4)
5	8 (2.8)
>5 In those who had at least 1 clinical event	18 (6.2)
No. of clinical events per patient, median (IQR), range	2 (1-16), 1-66
Time to clinical event after ICU discharge, median (IQR), range, d	6 (0-103), 0-115
Clinical events <7 days after ICU, No. (%) of 597 events	300 (50.3)
Clinical events <14 days after ICU, No. (%) of 597 events	401 (67.2)
Categorization of event, No. (%) of 597 events	
Cardiovascular	53 (8.9)
Neurological	144 (24.1)
Gastrointestinal	16 (2.7)
Renal	23 (3.9)
Respiratory	25 (4.2)
Sepsis	113 (18.9)
Blood/blood products	209 (35.0)
Other	24 (4.0)
Clinical event episodes included in major event, No. (%) of 597 events	
Delirium	131 (21.9)
Pneumonia	40 (6.7)
Deep venous thrombosis/pulmonary thromboembolism	40 (6.7)
Urinary tract infection	3 (0.5)
Myocardial infarction	1 (0.2)
New-onset arrhythmia	4 (0.7)
Catheter-related bloodstream infection	8 (1.3)
Patients with at least 1 major clinical adverse event	185 (63.6)
No. of major clinical events per patient (n = 185), median (IQR), range	2 (1-8), 1-43

Abbreviations: ICU, intensive care unit; IQR, interquartile range.

3 (3.0%) patients died. Only 10 patients received palliative care, 3 at the time of the RRSA and 7 after it. Most RRSAs occurred during the first 7 days following ICU discharge.

A total of 192 patients (66%) experienced at least 1 clinical event during their stay in the general care area, with a median of 2 events (IQR, 1-16 events) per patient. The frequencies of each type of clinical event experienced during the stay in the step-down unit are summarized in Table 3. The median time after ICU discharge until the onset of a clinical event was 6 days (IQR, 0-103 days). Among all clinical events, 255 (43%) were MCAEs, the most common of which were delirium, pneumonia, thromboembolic disease, and urinary tract infection. More than 60% of patients experienced at least 1 MCAE. All clinical events that occurred after ICU discharge are summarized in Supplemental Table 5.

An RSSA-7 was associated with age, a diagnosis of sepsis at ICU admission, APACHE II and SOFA scores at ICU discharge, the APACHE III score at ICU admission, and the Charlson Comorbidity Index (Table 4). There was no association of RSSA-7 with CBT-24 rhythmicity at ICU discharge. Only age, sepsis at ICU admission, and Charlson Comorbidity Index were independent predictors of an RRSA-7. The predicted probability for sepsis at ICU admission for an RRSA-7 at the means of the covariates was 0.27 (95% CI, 0.18-0.35). Supplemental Figure 1 summarizes both sensitivity and specificity compared with probability cutoffs.

For MCAE-7, independent predictors were the absence of a rhythmic CBT-24, SOFA score at ICU discharge, Charlson comorbidity score, age, and male sex (Table 5). The predicted probability for the absence of a rhythmic temperature profile for an MCAE-7 at the means of the covariates was 0.60 (95% CI, 0.50-0.70). Supplemental Figure 2 summarizes sensitivity and specificity compared with probability cutoffs. Of the 147 MCAE-7 events, only 41 (28%) resulted in an RRSA-7.

Discussion

Results of the TAOPID study showed that the absence of CBT-24 rhythmicity was an independent predictor of MCAE-7, as were illness severity at discharge, comorbidities, age, and sex. Such relationships were less robust beyond 7 days after ICU discharge, and the lack of CBT rhythmicity had limited effect in predicting an RRSA-7.

Rhythmicity of physiological processes is a key element of homeostasis and is optimally coordinated with geophysical time.[27] Many rhythmic processes are commonly disrupted in patients in an ICU[1,3,4,28-34]; the degree of disruption is associated with increasing illness severity.[31] Recommendations are available for care routines and environments to facilitate circadian rhythms.[35,36] The effectiveness of therapies that attempt to normalize these timings and their benefit to critically ill patients have not been studied sufficiently. Our study demonstrates that, at least for temperature measurement, not all patients had a normal rhythmicity by the time of ICU discharge, which has implications for predicting MCAEs after ICU discharge.

Circadian rhythm dysfunction suggests an underlying abnormality or illness process.[37] Assessment of CRD can, however, be complex and expensive because of the need for repeated measurements of surrogate metabolic markers.[37] Body temperature is readily

measurable in the ICU, but apart from defining fever, patterns of temperature profiles have not been well defined in critically ill populations.[38]

Rapid response systems are generally reactive to alerts or parameters from various approaches to monitor vital signs,[39-42] though an RRSA does not always occur when a patient clinically deteriorates.[43] Many MCAEs may result in severe patient morbidity despite an RRSA not being called for all MCAEs. The performance of predictors for patient deterioration following ICU discharge are varied. Objective measures such as the level of C-reactive protein are better predictors than ICU admission type (medical, surgical, trauma), the timing of ICU discharge, SOFA score at ICU discharge, white cell count, or fibrinogen concentration.[44] Outreach systems for use after ICU discharge principally aim to preempt deterioration before abnormal physiological signs occur. Phenotypic profiling has utility in reducing ICU readmission rates within 48 hours but has not effected an overall change in patient outcome.[45] Existing scoring systems such as the National Early Warning Score have been predictive of clinical deterioration after an ICU stay,[46] and in particular for respiratory failure.[12,47] Our study did show consistent associations between SOFA score at discharge, MCAE-7, and RRSA-7. In the TAOPID study, we uniquely assessed CBT to objectively and simply predict patients' progress after ICU discharge. We found utility for it, however, only within the early post-ICU period, similar to findings from previous predictive studies of clinical deterioration.[12] This finding is relevant because it also defines a potential optimal time period for outreach services to patients who have been recently discharged from the ICU.

The relation between MCAE and the patient's sex may reflect a complex relationship between clinical outcomes, age, and sex[48]; women aged younger than 50 years have a lower adjusted mortality rate than men, who receive more intense treatment and have higher ICU readmission rates.[49-51] Hormonal differences may also influence responses to sepsis and hypoxia.[52,53] Illness specificity may be important, as adjusted mortality rates differ between the sexes for illnesses such as chronic obstructive pulmonary disease and ischemic heart disease.[48] Men may have higher morbidity than women after trauma.[48] Such effects may be reflected in the influence of male sex on the regression model, increasing the likelihood of an adverse clinical event.

Pragmatically, we used all temperature assessment modalities that were available within the last 24 hours of the ICU stay, as this process represents clinical reality. Measurements of CBT obtained with bladder catheter thermistors are not always used in the last days of an ICU stay, when the intensity and invasiveness of clinical monitoring may be reduced. Most patients, however, did have enough clinical measurements available to allow us to determine CBT rhythmicity. The temperature profile may be truncated with the

Table 4
Univariate and multivariate logistic regression models for rapid response system activation within 7 days of ICU discharge[a]

Logistic regression model	Odds ratio (95% CI)	*P*
Univariate		
Age, y	1.04 (1.02-1.06)	.001
Male sex (reference: female sex)	0.75 (0.42-1.33)	.32
Sepsis diagnosis at ICU admission	2.01 (1.17-3.60)	.01
APACHE II score		
ICU admission	1.05 (1.01-1.08)	.01
ICU discharge	1.07 (1.02-1.13)	.01
Core temperature not rhythmic at ICU discharge	1.58 (0.97-2.58)	.06
ICU length of stay, d	1.02 (0.99-1.05)	.16
Duration, d		
Invasive ventilation	1.00 (0.99-1.00)	.35
Inotropic therapy	1.00 (1.00-1.00)	.47
Ileus	1.00 (1.00-1.00)	.16
Continuous dialysis	1.00 (0.99-1.01)	.06
Sedation	1.00 (1.00-1.00)	.86
Acute renal failure diagnosis at ICU admission	1.64 (0.78-3.44)	.19
APACHE II chronic health conditions[b]		
Renal	2.18 (0.51-9.39)	.29
Respiratory	0.70 (0.08-6.14)	.75
Immunocompromised	1.19 (0.31-4.54)	.80
Liver	0.28 (0.04-2.23)	.23
Nonoperative or emergency postoperative patients	0.28 (0.02-4.52)	.37
APACHE III score at ICU admission	1.01 (1.01-1.02)	.002
SOFA score		
At ICU admission	1.07 (1.00-1.15)	.08
At ICU discharge	1.14 (1.03-1.27)	.02
Charlson Comorbidity Index		
Count	1.00 (1.00-1.00)	.77
Sum	1.25 (1.09-1.43)	.001
Type of ICU admission (reference: medical)		
Surgical	1.05 (0.40-2.78)	.92
Trauma	0.66 (0.30-1.46)	.31
Multivariate[c]		
Charlson Comorbidity Index	1.18 (1.02-1.36)	.02
Age, y	1.03 (1.01-1.05)	.006
Sepsis at ICU admission	2.02 (1.13-3.63)	.02

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

[a] Likelihood ratio χ^2=24.09, *P*<.001. Hosmer-Lemeshow goodness of fit χ^2=10.57, *P*=.23. Area under receiver operating characteristic curve=0.70.

[b] Cardiovascular completely predicted rapid response system activation within 7 days of ICU discharge.

[c] Stepwise forward inclusion of univariate associations where *P*<.25.

Table 5
Univariate and multivariate logistic regression models for major clinical adverse events within 7 days of ICU discharge[a]

Logistic regression model	Odds ratio (95% CI)	*P*
Univariate		
Age, y	1.02 (1.00-1.03)	.03
Male (reference: female sex)	1.62 (1.00-2.64)	.05
Sepsis diagnosis at ICU admission	0.71 (0.44-1.13)	.15
APACHE II score		
ICU admission	1.02 (0.99-1.04)	.29
ICU discharge	1.04 (0.34-1.17)	.10
Core temperature not rhythmic at ICU discharge	1.58 (0.97-2.58)	.06
ICU length of stay, d	1.03 (1.00-1.04)	.05
Duration, d		
Inotrope therapy	1.00 (1.00-1.00)	.07
Invasive mechanical ventilation	1.00 (1.00-1.00)	.05
Ileus	1.00 (0.99-1.00)	.86
Continuous dialysis	1.00 (0.99-1.00)	.88
Acute renal failure diagnosis at ICU admission	0.98 (0.50-1.90)	.94
APACHE II chronic health conditions		
Renal	1.65 (0.39-7.06)	.50
Cardiovascular	1.97 (0.18-22.00)	.58
Respiratory	0.98 (0.19-4.93)	.98
Immunocompromised	0.48 (0.14-1.62)	.23
Liver	0.83 (0.27-2.54)	.75
Nonoperative or emergency postoperative patients	1.02 (0.06-16.48)	.99
APACHE III score on ICU admission	1.02 (1.00-1.01)	.20
SOFA score		
ICU admission	1.01 (0.95-1.07)	.75
ICU discharge	1.10 (1.00-1.21)	.05
Charlson Comorbidity Index		
Count	0.97 (0.81-1.16)	.75
Sum	0.93 (0.83-1.05)	.24
Type of ICU admission (reference: medical)		
Surgical	0.57 (0.24-1.35)	.21
Trauma	1.60 (0.87-2.95)	.13
Multivariate[b]		
Core temperature not rhythmic at ICU discharge	1.78 (1.07-2.98)	.03
Charlson Comorbidity Index	0.87 (0.76-0.99)	.03
Age, y	1.02 (1.00-1.04)	.02
Male sex	1.72 (1.04-2.86)	.04
SOFA score at ICU discharge	1.10 (1.00-1.21)	.05

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit; SOFA, Sequential Organ Failure Assessment.

[a] Likelihood ratio $\chi^2 = 20.93$, $P < .002$. Hosmer-Lemeshow goodness of fit $\chi^2 = 2.74$, $P = .95$. Area under receiver operating characteristic curve = 0.65.
[b] Stepwise forward inclusion of univariate associations when $P < .25$.

use of all clinically available routes of temperature measurement. As such, in this study we focused assessment on the dichotomized presence of temperature rhythmicity as this is more likely than amplitude or phase to be preserved across measurement methods.

Using regularly available data, we were able to predict patient deterioration. The limited comparison data available are from 24-hour temperature profiles of healthy patients with public domain data stratified by sex only. Despite a lack of age matching, normal temperature profiles are still rhythmic across all age groups. We expected that temperature profiles from similarly aged healthy people, used as controls for comparison, would not be arrhythmic or phase reversed, as is the case with temperature profiles in many ICU patients. The TAOPID study was an initial exploration of CBT-24 as a simple, readily available, and objective measure of the cyclic character of temperature profile at ICU discharge and its potential clinical utility. When CBT is collected as part of an electronic clinical information system, its inclusion in scoring systems that are used for predicting clinical deterioration after ICU discharge could provide an additional assessment when stratifying the need for post-ICU follow-up.

Conclusion

The TAOPID study supports the use of readily available CBT-24 measurements along with illness severity at ICU discharge to assist in stratifying the risk of subsequent deterioration of patients during care in a step-down unit.

FINANCIAL DISCLOSURES
None reported.

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Supplemental Table 1
Onset of clinical adverse events in general care areas after discharge from the intensive care unit[25]

Nosocomial Infection of a defined organ system, wound or catheter related, requiring antibiotic therapy (*ICD-10* clinical code)
Myocardial infarction both ST elevation and non-ST elevation/ischemia/arrhythmia, either supraventricular or ventricular, requiring clinical treatment (*ICD-10* clinical code)
Deep venous thrombosis/pulmonary thromboembolism proven by radiology and requiring treatment (*ICD-10* clinical code)
Confusion/delirium assessed through bedside nursing assessment of level of consciousness
Insulin therapy for blood glucose control in a patient with previously unknown diabetes
Peak alkaline transaminase and total bilirubin levels on routine biochemical assessment to document the presence of potential hepatic dysfunction
Ileus defined as a clinical description of abdominal distension, need for nasogastric drainage and cessation of enteral feedings
Hyponatremia (sodium ≤130 mmol/L)
Worsening estimated glomerular filtration rate
Need for blood transfusion

Abbreviation: *ICD-10, International Statistical Classification of Diseases, Tenth Revision.*

Supplemental Table 2
Drug classes prescribed per patient within 24 hours of discharge from the intensive care unit

Drug class	No. (%) of 291 patients
Angiotensin-converting enzyme/all inhibitors	22 (7.6)
Antiarrhythmics	12 (4.1)
Antibiotics	185 (63.6)
Anticoagulants	236 (81.1)
Anticonvulsants	46 (15.8)
Antidepressants	26 (8.9)
Antiemetics	44 (15.1)
Antihypertensives	43 (14.8)
Benzodiazepines	67 (23.0)
β-Blockers	64 (22.0)
Bronchodilators	109 (37.5)
Diabetes medications	72 (24.7)
Diuretics	89 (30.6)
Digoxin	12 (4.1)
Fluids	128 (44.0)
H_2 antagonists	33 (11.3)
Inhaled corticosteroids	40 (13.7)
Lipid-lowering drugs	22 (7.6)
Major tranquilizers	52 (17.9)
Narcotics	132 (45.4)
Nonsteroidal anti-inflammatory drugs/Cox-2	42 (14.4)
Other immunosuppressants	7 (2.4)
Other medications	195 (67.0)
Acetaminophen	175 (60.1)
Prescribed nutrition	159 (54.6)
Proton pump inhibitors	160 (55.0)
Sedatives	58 (19.9)
Systemic corticosteroids	65 (22.3)

Supplemental Table 3
Summary of Charlson comorbidities

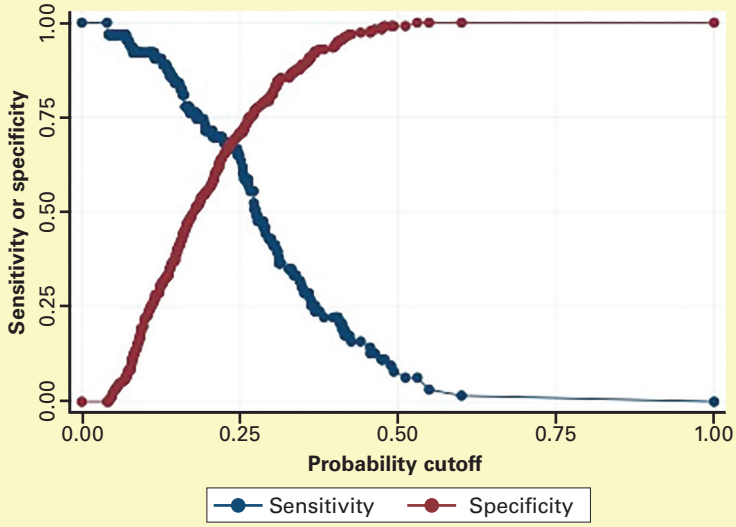
Charlson comorbidity	No. (%) of 291 patients
Cardiovascular Hypertension	98 (33.7)
Respiratory Pulmonary disease/asthma	70 (24.1)
None	64 (22.0)
Mood Depression	63 (21.6)
Mood Other psychiatric disease	48 (16.5)
Endocrine Diabetes mellitus (no end-organ disease)	43 (14.8)
Cardiovascular Congestive heart failure	28 (9.7)
Cancer Nonmetastatic (solid organ)	22 (7.6)
Gastroenterology Liver disease (mild)	21 (7.2)
Cardiovascular Cerebrovascular disease/transient ischemic attack	19 (6.5)
Gastroenterology Liver disease (moderate/severe)	17 (5.8)
Hematology Anticoagulation: warfarin/novel oral anticoagulants	16 (5.5)
Hematology Anticoagulation: platelet IIa/IIIb inhibitors	14 (4.8)
Renal Moderate/severe renal disease	13 (4.5)
Cancer Leukemia	9 (3.1)
Gastroenterology Gastric/peptic ulcer	9 (3.1)
Cardiovascular Peripheral vascular disease/bypass	8 (2.7)
Cardiovascular Myocardial infarction	7 (2.4)
Endocrine Diabetes mellitus (with end-organ disease)	7 (2.4)
Dermatology Skin ulcers/cellulitis	6 (2.1)
Infectious HIV/AIDS	3 (1.0)
Central nervous system Hemiplegia	2 (0.7)
Cancer Lymphoma	2 (0.7)

Supplemental Table 4
Temperature sources and frequency of use among 289 patients during their final 24 hours in the intensive care unit

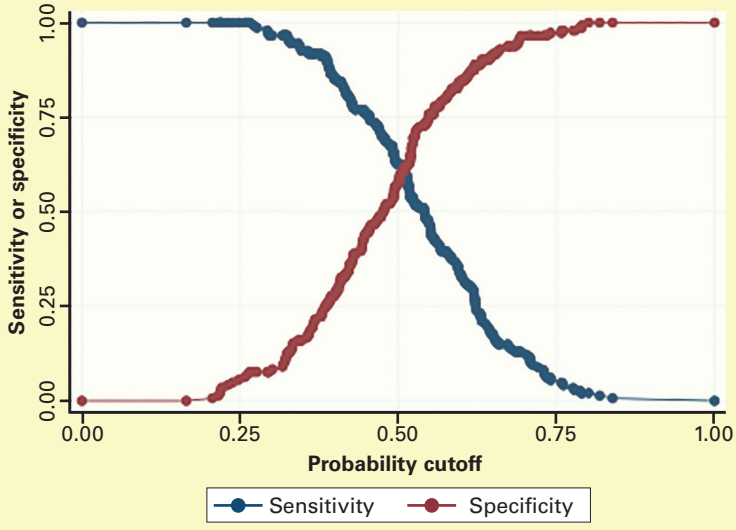
Parameter	Median (IQR), range
No. of temperature measurements per patient	22 (11-24), 6-35
No. of temperature measurements per patient by site	
Urinary bladder	23 (21-25), 1-35
Axillary	7 (2-8), 1-16
Nasopharyngeal	14 (7-19), 1-23
Tympanic	4 (1-9), 1-10
Esophageal	3 (3-10), 2-22
Oral	1 (1-1), 1-1
Blood	1 (1-1), 1-1
Rectal	1 (1-1), 1-1
Percentage of temperature measurements available per patient by site	
Urinary bladder	100 (100-100), 10-100
Axillary	100 (13-100), 4-100
Nasopharyngeal	70 (37-87), 13-96
Tympanic	46 (17-100), 4-100
Esophageal	33 (25-56), 8-96
Oral	9 (5-13), 5-13
Blood	7 (5-8), 5-8
Rectal	2 (2-2), 2-2

Supplemental Table 5
Clinical events occurring in general care area after intensive care unit discharge

Clinical event	No. (%) of 597 events
Acute myocardial infarction	1 (0.2)
Acute dialysis	4 (0.7)
Acute kidney injury	17 (2.9)
Acute noninvasive ventilation	15 (2.5)
Anaphylaxis	1 (0.2)
Bloodstream infection	8 (1.3)
Deep venous thrombosis	28 (4.7)
Delirium	131 (21.9)
Dysrhythmia	4 (0.7)
Exacerbation of airway disease	1 (0.2)
Gastrointestinal obstruction/ileus	9 (1.5)
Gastrointestinal infection	6 (1.0)
New insulin therapy (no diabetes previously)	7 (1.2)
New-onset liver dysfunction	1 (0.2)
Pneumonia	40 (6.7)
Pulmonary emboli	12 (2.0)
Red blood cell transfusion	144 (24.1)
Seizure	3 (0.5)
Soft-tissue infection	18 (3.0)
Stroke	3 (0.5)
Urinary tract infection	31 (5.2)
Other events	
Platelet transfusion	61 (10.2)
Other blood product transfusion	4 (0.7)
Event categories	
Neurological	144 (24.1)
Renal	23 (3.9)
Respiratory	25 (4.2)
Sepsis	113 (18.9)
Gastrointestinal	16 (2.7)
Cardiovascular	53 (8.9)



Supplemental Figure 1 Sensitivity and specificity plotted against the probability cutoffs for rapid response system activations within 7 days of discharge from the intensive care unit.



Supplemental Figure 2 Sensitivity and specificity plotted against the probability cutoffs for medical clinical adverse events within 7 days of discharge from the intensive care unit.