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Exacerbation of circadian rhythms of core body temperature and sepsis in trauma patients

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Abstract

Purpose: This study aimed to describe by mathematical modeling an accurate course of core body temperature (CBT) in severe trauma patients and its relation to sepsis.

Methods: In a cohort of severe trauma, the CBT measurements were collected for 24 hours on day 2 after admission and rhythmicity assessed by Fourier transform and Cosinor analysis to describe circadian features (frequency and amplitude). CBT was compared between patients who developed sepsis or not during the early ICU stay.

Results: 33 patients were included in this analysis. 24 patients (73%) had a predominant rhythm of 24 hours (period). The main period was lower in the 9 remaining patients (6 of 12 hours, 1 of 8 hours, and 2 of 6 hours). Other significant frequencies of oscillation (second and third frequencies) were found, which showed an association of several well-marked rhythms. Patients with sepsis (n=12) had a significantly higher level of CBT, but also more intense rhythms and higher amplitudes of CBT.

Conclusion: Trauma patients exhibit complex temperature circadian rhythms. Early exacerbation of the temperature rhythmicity (in frequency and amplitude) is associated with the development of sepsis. This observation accentuates the concept of circadian disruption and sepsis in ICU patients.

Keywords: Circadian rhythm; Chronobiology disorders; Trauma; Temperature; Sepsis; Intensive Care Units.

Abbreviations

CBT: core body temperature

ICU: intensive care unit

ISS: injury severity score

ANOVA: analysis of variance

SAPS2: simplified acute physiology score 2

SOFA: sequential organ failure assessment score

Introduction

Circadian rhythms are well recognized as regulators of host defense [1] and are involved in the immune response of the critically ill patients [2]. Circadian disruption of the core body temperature (CBT) in the intensive care unit (ICU) patients has been previously described [3-6] but the precise fitting of the CBT curve and the circadian features (frequency and amplitude) have been poor reported. In this ancillary study, we applied mathematical modeling to the CBT time-series in severe trauma patients in the ICU with the aim to describe an accurate CBT course and its relation to sepsis.

Methods

Study design and patient selection

This study is an ancillary analysis from our previously published study on circadian rhythm in trauma patients [7]. The original study was conducted on 38 severe trauma patients defined by an injury severity score (ISS)>15 who required mechanical ventilation for at least 24 hours. The circadian rhythm blood markers were then analyzed at day 2 according to the development of sepsis. All patients or a legal surrogate consented to participate in the study. The protocol was approved by our local ethics committee of Sud-Méditerranée I (ID RCB 2014-A01378-39) and registered on ClinicalTrial (NCT02307747).

Temperature collection

The CBT measurements were assessed (extracted from our ICU numerical database) at day 2 after admission for a period of 24 hours. Only the CBT measurements (1 value every 5 seconds) obtained using a Foley urinary catheter (400 TM temperature sensor, Covidien™, Boulder, USA) were collected.

Fourier transform and Cosinor analysis

All analyses were performed with the public software R version 3.5.1. To determine the most probable time of temporal oscillation (period) of the CBT, a spectral resolution method (Fourier transform) was used [8]. From this method a frequency spectrum revealed the most accurate periods of the CBT in each individual (the intensity of the frequency reflects the sinuosity of the CBT curve with period = 1/frequency). We extracted the first 3 best frequencies estimated by the transform and calculated the other circadian parameters with the cosinor analysis (*cosinor* package in R) for each frequency. This analysis used the least squares method to fit a sine wave to a time-series specified as $y = mes + amp \times \cos(2\pi(t - \phi)/period)$, where y was the CBT, t represented time-of-day in decimal hour, *mes* represented the mesor, *amp* the amplitude, ϕ the acrophase (peak time) of the circadian rhythm. The MESOR (Midline Estimating Statistic Of Rhythm) represents the mean of the modeled rhythm over the time studied. The amplitude is the difference between mesor and the acrophase (the half of the difference between the lowest and the highest value).

Central body temperature fitting curves were obtained using a regression model (glm function of the stats package in R) of the cosine function with a 24-hr period as follow:

$model = y \sim \cos(2\pi(t)/24) + \sin(2\pi(t)/24)$,

and for the other periods (lower than 24-hr), included in the model as follow:

- for the second frequency:

$$model2 = model + 24*frequency*\cos(2\pi(t)/24) + 24*frequency*\sin(2\pi(t)/24)$$

- for the third frequency:

$$model3 = model2 + 24*frequency*\cos(2\pi(t)/24) + 24*frequency*\sin(2\pi(t)/24)$$

Statistical analysis

Continuous variables were expressed as median values [interquartile] and comparison between the 2 groups (according to the sepsis here) were performed using the Mann-Whitney test. Comparison between the 3 groups (according to the three frequencies here) were performed using the ANOVA analysis of variance.

Results

Population

Of the 38 patients in the original study, 33 patients were included in this analysis (5 excluded due to a lack of CBT data or no central temperature measurements). The population was similar as that of the original study: age of 31 years [23-43], a majority of men (79%) with an ISS score of 34 [26-41], a SAPS2 of 43 ±15, and a SOFA score of 4 [3-5] at day 2. The majority of these patients had head trauma (82%) and received sedative agents on day 2 (69%).

Core Body Temperature rhythms

The spectral analyses of the CBT revealed 24 (73%) patients had a predominant rhythm of 24 hours (period). However, the main period was lower in the 9 remaining patients (6 of 12 hours, 1 of 8 hours, and 2 of 6 hours). In most patients other significant frequencies of oscillation (second and third frequencies) were found, which showed an association of several well-marked rhythms.

Panels A, B, and C in **Figure 1** illustrate three characteristic examples of the CBT profiles. Patient A had a unique period of 24 hours with no other significant associated rhythm. Patient B had the main period at 24 hours but had additionally significant second and third frequencies as revealed by the intensity of the peaks on the spectral analysis obtained by Fourier transform. Significant rhythms of 12 and 6 hours added up to the main period of 24 hours. Patient C had the main period at 6 hours and an additional second rhythm of 24 hours but no significant third frequency of oscillation.

Panels A, B, and C in **Figure 2** show that the period of CBT, spectral intensity, and amplitude of CBT respectively decreased from the first to the third frequency revealed by the Fourier transform ($p<0.001$ for each of the situations).

*Core Body Temperature rhythms according to sepsis (**Table 1**)*

Twelve (36%) patients developed at least 1 sepsis episode during the study period. As in the original study, no significant differences between groups were found, except for males who developed sepsis more frequently ($p=0.02$).

When the period was fixed at 24 hours for all patients in the cosinor model, acrophase (time at the highest value of CBT) peaked at 18.2 hours [09.4-20.4], without influence of sepsis ($p=0.86$). The intensities of the frequency peaks in the spectral analysis were generally higher in the septic patients, revealing more precise and stronger CBT rhythms in the latter. The frequencies (periods) were not different between groups for the first, second, and third oscillation intensity revealed by the Fourier transform. Patients who will develop sepsis had significantly higher mesor at the first and second frequencies, and higher amplitudes of CBT at each frequency of oscillation. The amplitude differences between the groups were even greater in the second and especially the third frequencies.

Discussion

Trauma patients exhibit complex temperature circadian rhythms. Early exacerbation of the temperature rhythmicity (in frequency and amplitude) is associated with the development of sepsis. To our knowledge, this is the first description of the presence of multiple rhythms in one marker of circadian rhythm in ICU patients. This observation highlights the complexity of the circadian rhythms and the concept of circadian disruption in ICU patients [2]. We suggest the application of a precise mathematical model may be more important than describing the absence of 24-hours rhythm, which actually could be related to different frequencies of oscillation.

As stated earlier, these findings show an association between circadian disruption and sepsis [1,7,9]. We observed a higher level, intensity, and amplitude of CBT in the patients who will develop sepsis. In a previous study, they described abnormal patterns and larger temperature deviation as an early predictor of sepsis in afebrile patients [4].

Circadian disruption of CBT is a marker of severity and a consequence of a severe injury. Nonetheless, it may also influence the expression of main clock genes as described in a model of mammalian cells [10] and potentially impact other major functions of the organism.

These observations have to be confirmed in larger prospective studies to specifically assess the weight of confounding factors such as acetaminophen which could influence the core body temperature.

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Legends

Figure 1: Examples of Fourier transform and Cosinor regression of the core body temperature.

Three characteristic examples (**A**, **B**, and **C**) of core body temperature rhythms in trauma patients. The graphs on the left represent the period spectra from the Fourier transform. The first 3 most intense periods (corresponding to the most accurate frequencies) are targeted by the arrows (red: first frequency, green: second frequency, black: third frequency). On the right graphs, grey dots represent the 24-hour core body temperature measured in each individual. Red, green, and black curves represent the regression fitting of the core body temperature using a cosinor function according to the first 3 most accurate periods from the Fourier transform (first, second, and third period respectively).

The amplitudes revealed by Cosinor analysis at each frequency were as follow: Patient A: 0.95°C, 0.17°C, 0.05°C; Patient B: 0.4°C, 0.24°C, 0.16°C; Patient C: 0.27°C, 0.25°C, 0.07°C, for the first, second, and third frequency respectively.

Figure 2: Periods, intensities, and amplitudes according to the first 3 best frequencies obtained by Fourier transform and cosinor analysis.

The graph **D** represents the distribution of the period of the first 3 best frequencies estimated by the Fourier transform. Lines binds the dots from one individual.

The graph **E** represents the distribution of the intensities of the first 3 best frequencies estimated by the Fourier transform.

The graph **F** represents the distribution of the temperature amplitude in each individual obtained by the cosinor analysis according to the period for the first 3 best frequencies estimated by the Fourier transform.

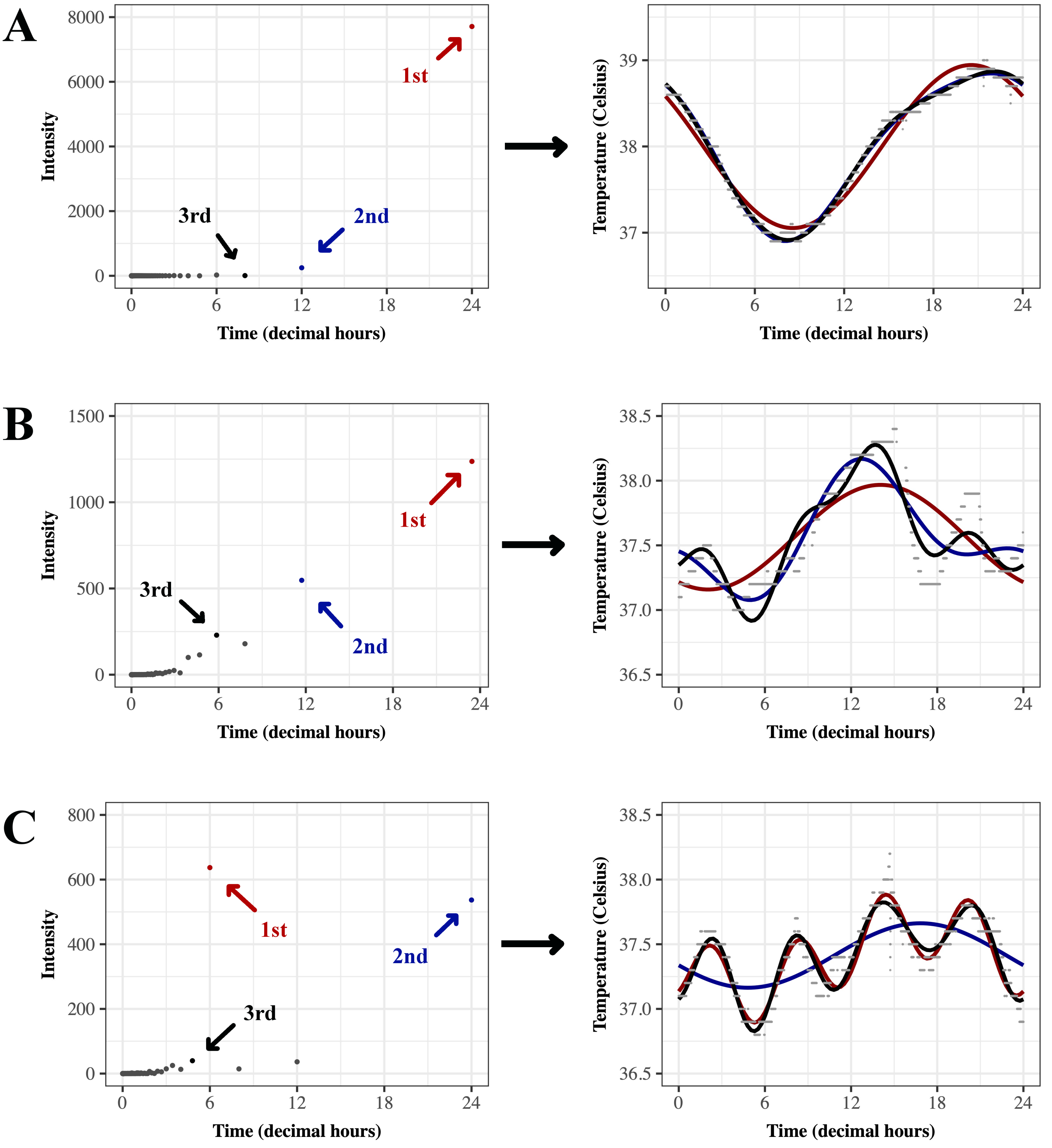
The boxplots correspond to the medians with inter-quartile range (IQR) (distance between the first and third quartiles); the lower and upper whiskers extend from the hinge to the lowest and highest (respectively) values that are within 1.5xIQR of the hinge.

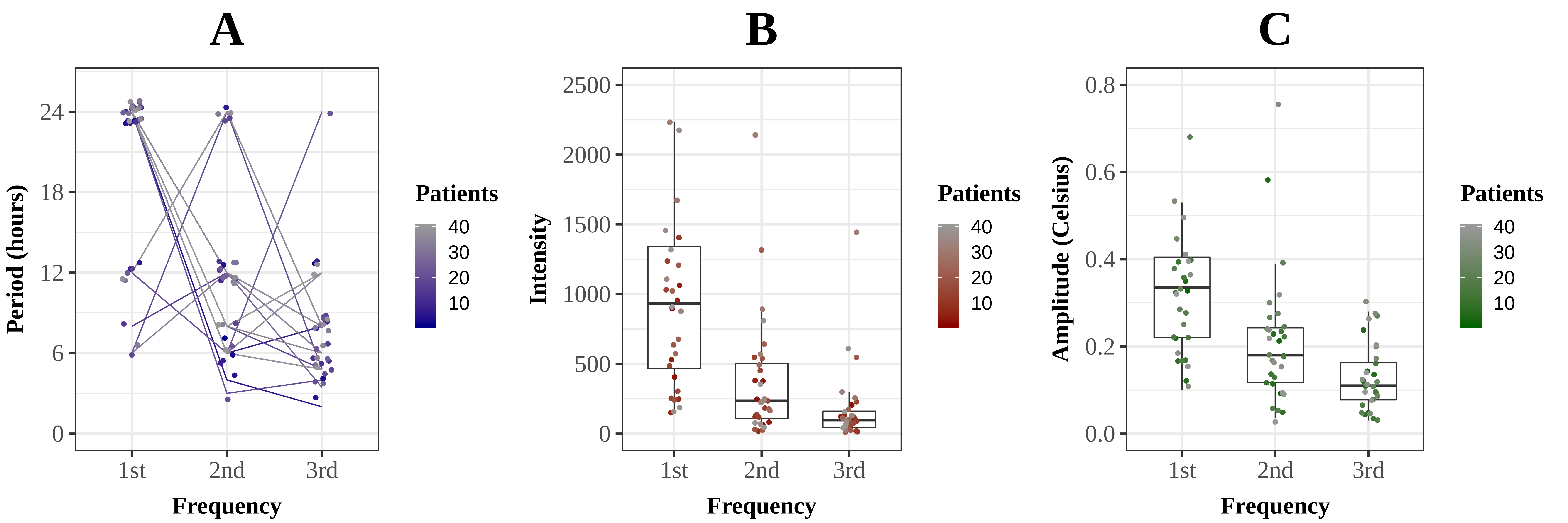
Table

	Total	Non-septic	Septic	p value
Patients	n= 33 (100)	n=21 (64)	n=12 (36)	
Period fixed at 24 hours				
Mesor (Celsius)	37.56 [37.41-37.83]	37.50 [37.28-37.69]	37.75 [37.61-37.91]	0.03
Amplitude (Celsius)	0.33 [0.19-0.40]	0.25 [0.17-0.37]	0.38 [0.30-0.57]	0.04
Acrophase (hours)	18.23 [9.41-20.43]	18.29 [16.59-20.44]	16.37 [07.28-20.48]	0.86
Period spectrum intensity				
AUC (Unit.hour)	7461 [4209-10828]	5183 [2839-9808]	9145 [7120-18987]	0.07
First frequency				
Intensity (unit)	932 [466-1340]	605 [252-1235]	1069 [891-1798]	0.05
Period (hours)	24 [12-24]	24 [21-24]	24[12-24]	0.67
Mesor (Celsius)	37.56 [37.41-37.83]	37.50 [37.28-37.69]	37.75 [37.61-37.94]	0.04
Amplitude (Celsius)	0.33 [0.22-0.40]	0.26 [0.18-0.37]	0.38 [0.33-0.51]	0.047
Second frequency				
Intensity (unit)	236 [110-504]	209 [75-360]	437 [167-629]	0.09
Period (hours)	12 [7.5-12]	12 [6-12]	12 [8-12]	0.68
Mesor (Celsius)	37.55 [37.41-37.83]	37.50 [37.23-37.69]	37.74 [37.60-37.92]	0.04
Amplitude (Celsius)	0.18 [0.12-0.24]	0.16 [0.09-0.21]	0.24 [0.18-0.31]	0.03
Third frequency				
Intensity (unit)	97 [45-162]	79 [36-110]	152 [100-267]	0.02
Period (hours)	7 [6-8]	6 [5.7-8]	8 [6-8]	0.63
Mesor (Celsius)	37.56 [37.38-37.83]	37.50 [37.25-37.75]	37.74 [37.52-37.94]	0.11
Amplitude (Celsius)	0.11 [0.08-0.16]	0.09 [0.05-0.12]	0.17 [0.12-0.24]	0.007

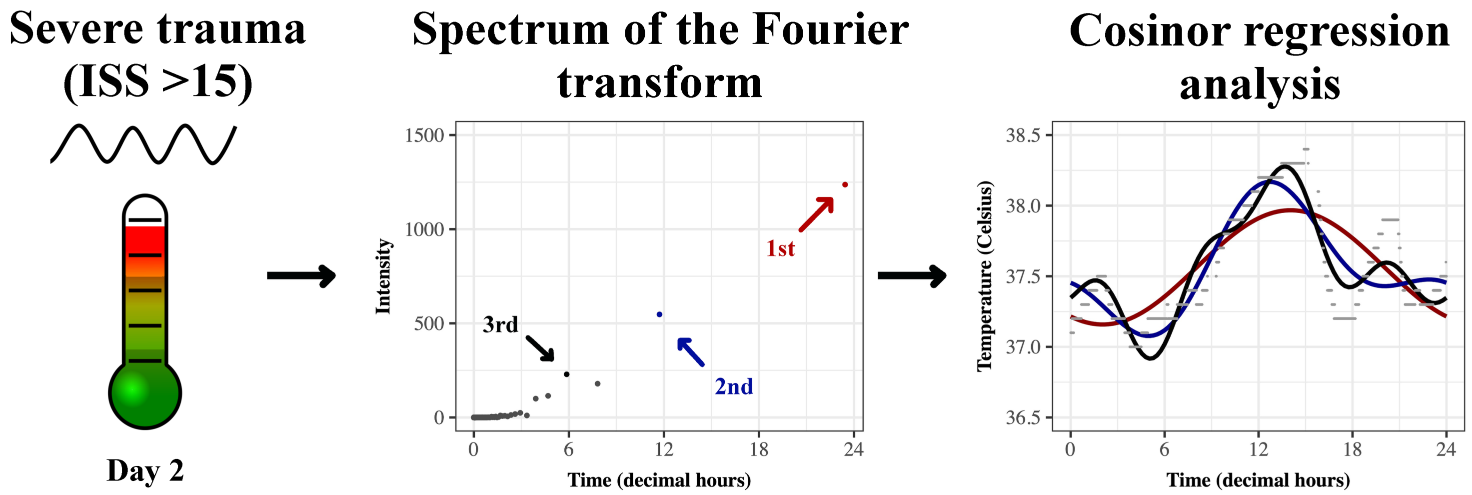
Table 1: Circadian rhythm parameters (mesor, amplitude, acrophase) of the temperature according to the septic and non-septic trauma patients and the Fourier transform. The circadian rhythm parameters were obtained by cosinor analysis including in the model a fixed period at 24 hours (first 3 lines) or the periods for the first three best frequencies estimate by the Fourier transform.

AUC: Area under the curve calculated by the integral of the spectrum curve.


A
B
C
Intensity
Time (decimal hours)
Temperature (Celsius)
1st
2nd
3rd
8000
6000
4000
2000
1500
1000
500
800
600
400
200
0
6
12
18
24
39
38
37
38.5
38.0
37.5
37.0
36.5



A
B
C
Period (hours)
24
18
12
6
0
Intensity
2500
2000
1500
1000
500
0
Amplitude (Celsius)
0.8
0.6
0.4
0.2
0.0
1st
2nd
3rd
Frequency
Patients
40
30
20
10


Severe trauma
(ISS >15)
Day 2
Spectrum of the Fourier transform
Intensity
1500
1000
500
0
0
6
12
18
24
Time (decimal hours)
1st
2nd
3rd
Cosinor regression analysis
Temperature (Celsius)
38.5
38.0
37.5
37.0
36.5
0
6
12
18
24
Time (decimal hours)