Heart Rate Variability Using The Analgesia Nociception Index as A Predictor of Illness Severity and Mortality in Critically Ill Patients with COVID-19.

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Research

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Abstract

Introduction A balance between the autonomic nervous system and the immune system against SARS-COV-2 is critical in the resolution of its severe macrophage proinflammatory activation.

To demonstrate that most severely ill COVID-19 patients will show a depletion of the sympathetic nervous system and a predominance of parasympathetic tone. We hypothesized that a low energy of an autonomic nervous system and a high level of the high frequency component of heart rate variability may be related to the number of proinflammatory cytokines and could have a predictive value in terms of severity and mortality in critically ill patients suffering from COVID-19;

Materials and Methods Single-centre, prospective, observational pilot study which included COVID-19 patients admitted to the Surgical Intensive Care Unit. High frequency (HF) component of heart rate variability (HRV) and energy of the autonomic nervous system were recorded using analgesia nociception index monitor (ANI). To estimate the severity and mortality we used the SOFA score and the date of discharge or date of death.

Results A total of fourteen patients were finally included in the study. High-frequency component of heart rate variability (ANIm) were higher in the non-survivor group (p = 0.003) and were correlated with higher IL-6 levels (p = 0.002) Energy was inversely correlated with SOFA (p = 0.029). Limit value at 80 of ANIm, predicted mortalities with the sensitivity of 100% and specificity of 85.7%. In the case of energy, a limit value of 0.41 predicted mortality with all predictive values of 71.4%.

Conclusion The different components of the spectral analysis of HRV allow us to infer the association between the autonomic nervous system and critically ill patients' immune system. A low autonomic nervous system activity and a predominance of the parasympathetic system due to sympathetic depletion in patients are associated with a worse prognosis and higher mortality.

Introduction

Since the pandemic started in early 2020, critically ill patients suffering from COVID-19 on mechanical ventilation have become one of the most challenging problems in intensive care units around the world [1]

The inflammatory reflex is the body's first defense against any infection, and any dysregulation of the body's homeostasis can lead to the death of individuals suffering from COVID-19 [2]. An efficient and balanced immune response against SARS-COV-2 appears to be critical in the resolution of the severe macrophage proinflammatory activation caused by the virus [3,4].

The autonomic nervous system (ANS) is responsible for the regulation of this inflammatory reflex, something that happens through the vagus nerve and the anti-inflammatory cholinergic pathway, and that is essential to the maintenance of this homeostasis [5,6].

Heart rate variability (HRV) refers to the variation between one heartbeat and the next, a process that is influenced by different components of the ANS, including breathing (respiratory sinus arrhythmia) and other physiological factors [7-9].

Analysis of HRV is a non-invasive method that evaluates the activity of the ANS [7, 8]. To do this, it performs a spectral analysis of the different spectral bands of HRV taken from a patient's electrocardiogram (ECG). The high-frequency component (HF between 0.15 Hz and 0.4 Hz) is mediated by the parasympathetic nervous system or vagal tone; the low-frequency component (LF between 0.15 to 0.04 Hz) is mainly influenced by baroreflex mechanisms and the sympathetic nervous system; and, lastly, the very low-frequency component (VLF between 0.04 to 0.003 Hz) is influenced by thermoregulation and different hormonal factors [9]. The total power of the RR interval variability encompasses the sum of all spectral bands and represents the total activity of the ANS [7-9].

There is a strong scientific evidence that demonstrates the usefulness of monitoring HRV in critically ill patients [9,10]. Many papers conclude that critically ill patients with lower HRV and lower total activity of the ANS (total power) have a greater number of complications and higher mortality [9-13].

They also show that, in particular, low autonomic activity with depletion of the sympathetic component (LF) and proportionally greater parasympathetic tone (HF) can predict the risk of developing respiratory distress (ARDS) in patients on mechanical ventilation, the success or failure of removal of this support, and mortality in these patients [14,15].

The analysis of HRV has also proven to be a crucial tool for the management of nociception in both surgical and critically ill patients [7,8,16,17]. Up to this point, this is the first study that sets out to analyze the HF component of HRV and the energy (total power) values as a prospective predictor for critically ill patients, and in particular for COVID-19 patients who are on mechanical ventilation.

We hypothesized that a low energy level and a high level of HF component of HRV could have a predictive value in terms of severity and mortality in critically ill patients suffering from SARS-COV-2; furthermore, we hypothesized that these values might be related to the number of proinflammatory cytokines, such as IL-6, C-reactive protein (CRP) and procalcitonin.

The main objective of this study is to demonstrate that the most severely ill COVID-19 patients will show greater dysregulation of the ANS, with a significant depletion of the sympathetic nervous system and a slight predominance of vagal tone, reflecting the remaining compensatory anti-inflammatory response.

Materials And Methods

Study Design & Inclusion/Exclusion Criteria

A single-centre, prospective, observational study was designed, which included COVID-19 patients admitted to the Surgical Intensive Care Unit of the Mostoles General University Hospital in Madrid between April and May 2020.

Given the nature of the study, patient inclusion was decided based on a sequential review of cases in the planned inclusion period. This study was performed in line with the principles of the Declaration of Helsinki and it was approved by the Research Ethics Committee of the site with registration code No. 2020/035.

Inclusion criteria were defined as follows: patients over 18 years of age, on mechanical ventilation, diagnosed with COVID-19 by a positive polymerase chain reaction (PCR) test for SARS-COV-2, and informed consent signed by the family. Exclusion criteria included: patients with a history of cardiac arrhythmia.

Patient Population and Anesthesia

On admission to our unit, all patients were monitored with the following: ECG, invasive blood pressure, oxygen saturation, and capnography. Sedoanalgesia was maintained using continuous infusions of different drugs, according to usual department protocol.

This protocol includes midazolam (0.03 - 0.2 mg.kg.hour-1), morphine (0.5 - 5 mg.hour-1), propofol (0.5 - 4 mg.kg.hour-1), remifentanil (0.05 - 0.2 mcg.kg.min-1), and/or dexmedetomidine (0.4 - 1.4 mcg.kg.min-1). In cases where neuromuscular blocking was needed, we used a continuous perfusion of cisatracurium (0.06 - 0.3 mg.kg.hour-1) or rocuronium (0.3 - 0.6 mg.kg.hour -1). Mechanical ventilation, by means of orotracheal intubation or tracheostomy, was personalized for each patient according to severity of illness and gasometric analytical parameters, as per the usual department protocols.

Measurements and Data Handling

As demographic data, the age, gender, and weight of the patients were recorded. Drugs used for sedoanalgesia, neuromuscular blocking drugs, and the need for vasoactive drugs (norepinephrine and/or dobutamine) were also recorded. To assess the degree of sedation, we used the Richmond Agitation-Sedation scale (RASS) [8], and to estimate the severity, we used the SOFA score (Sequential Organ Failure Assessment), validated for critically ill patients [11].

Also, data on ventilatory parameters (ventilatory mode, tidal volume, respiratory rate, and positive pressure at the end of expiration [PEEP]) were collected, as well as data for IL-6, CRP, and procalcitonin from the blood tests.

The high-frequency component of HRV and energy level (total power) were recorded using the analgesia nociception index monitor (ANI monitor, MDoloris Medical Systems, Lille, France). ANI monitor provides a number from 0 to 100, which is a percentage estimate of the balance between the parasympathetic nervous system (HFnu) and the added activity of the different spectral components, i.e., the total power or energy [7-9].

Energy and ANIm, i.e., the mean ANI value of the last 2 minutes, were recorded in the morning before daily washing with specific electrodes placed on the patient's chest or back, depending on whether they were in

a supine or prone position.

Subsequently, after 30 days, the patient's electronic medical record was checked and the date of hospital admission, date of admission to ICU, and date of discharge to hospital facility or date of death were recorded.

<u>Statistical Analysis</u>

To analyze the data, non-parametric tests were used. In the descriptive analysis of the data, the median and quartiles (first and third quartiles) were used. For the study of homogeneity of the sample and comparison of medians, the U-Mann-Whitney and Wilcoxon tests were performed. A Spearman's Rho correlation test was used to detect the bivariate relationship between variables. To find a threshold value to attempt to predict the risk of mortality and for the calculation of diagnostic accuracy, the corresponding receiver operating characteristic (ROC) curves were analyzed for both the ANIm value and the energy value.

Differences in the p-value of <0.05 were considered to be statistically significant. The different analyses were carried out using commands from the basic "stats" package of Software "R", version 3.1.2.

Results

During the data collection period, 16 patients were recruited, 2 of whom were excluded due to missing data as a result of a transfer to a different medical facility. A total of 14 patients were finally included in the study, with 7 patients belonging to the survivor group and 7 others belonging to the non-survivor group.

The differences between groups are shown in Table 1. The only differences in the groups were in terms of the use of neuromuscular blockers (p = 0.029), the RASS scale (p = 0.021) and PEEP value (p = 0.032). Also, the SOFA scores between the two groups were statistically different, with a p-value = 0.031, Mann-Whitney test; survivor group = 3 (2; 6), non-survivor group = 8 (3; 9).

The ANIm figures were considerably higher in the deceased group, as reflected in Figure 1, with a p-value = 0.003, Mann-Whitney test; survivor group = 64% (53; 74), non-survivor group 93% (89; 99). However, in terms of the energy figures, although lower in the non-survivor group (Figure 2), there are no statistically significant differences, p value = 0.225, Mann-Whitney test; survivor group = 0.57 (0.3; 0.63), non-survivor group 0.18 (0.13; 0.71).

Looking closer at the correlation between ANIm and energy with respect to the SOFA score, it was discovered that the ANIm value was not statistically correlated (p = 0.184, Spearman's Rho test). However, the energy itself was inversely correlated with the SOFA score (p = 0.029, Spearman's Rho test), in other words, patients with lower energy presented with greater severity of illness and a worse prognosis.

On the other hand, when analyzing inflammatory cytokines (IL-6, PCR, procalcitonin), it was discovered that the energy levels were not statistically correlated with any of them. However, higher ANIm levels were statistically correlated with higher IL-6 levels (p = 0.002, Spearman's Rho test). There was no such relationship with the rest of the cytokines, such as PCR (p = 0.4, Spearman's Rho test) or procalcitonin (p = 0.944, Spearman's Rho test).

For the ANIm value, we found that a limit value of 80 predicted mortalities with a sensitivity of 100%, a specificity of 85.7%, a positive predictive value of 87.5%, and a negative predictive value of 100% (Figure 1). In the case of energy, a limit value of 0.41 predicted mortality with a sensitivity of 71.4%, a specificity of 71.4%, a positive predictive value of 71.4%, and a negative predictive value of 71.4% (Figure 2).

If we look specifically at the non-survivor group, patients with worse SOFA scores presented with fewer survival days (p = 0.040, Spearman's Rho test). Also, it was found not only that the energy and the SOFA scores correlated (p = 0.029, Spearman´s Rho test), but that patients with lower energy values had fewer survival days (p = 0.031, Spearman's Rho test).

<u>Sub-analysis in RASS - 4 / - 5 Patients</u>

Although the distribution of drugs between the groups was homogeneous (Table 1), to minimize the bias that may occur between ANI monitor values, drug dosage, and the RASS, a sub-analysis was carried out only for patients with RASS -4/ -5. Three patients in the survivor group were removed from the sub-analysis (survivor group = 4 and non-survivor group = 7). In this way, all existing differences in homogeneity between the groups were eliminated (Table 2).

In the sub-analysis in patients with RASS -4/-5, it was shown that the difference between groups in terms of the ANIm value and energy was much greater, (Figures 3 and 4), and that the capacity to predict prognosis and death using these two values was higher (Figures 3 and 4). In the case of ANIm, all its predictive values, for a limit value of 80, were 100%. In terms of energy in this group of patients, for a limit value of 0.41, sensitivity was 71.4%, specificity was 75%, the positive predictive value was 83.3%, and the negative predictive value was 60% (Figures 3 and 4).

Discussion

Considering the current evidence, it was clear that COVID-19 patients in a critical state who present with low autonomic nervous system tone, i.e., a lower energy value, suffer from a higher severity of illness and have a worse prognosis according to the predictive SOFA score. A depletion of sympathetic tone and proportionally greater vagal tone, in other words, a high ANIm, is associated with higher IL-6 levels and higher mortality.

In our patient sample, a high ANIm value above 80 and a low energy value below 0.41, especially in more sedated patients (RASS -4/-5), predicted mortality with very high sensitivity and specificity.

According to the available literature, this is the first study to analyze HRV in critically ill patients suffering from SARS-COV-2 who are on mechanical ventilation. It is also the only one so far that shows that COVID-19 patients with the worst prognosis and highest mortality present significant depletion of the ANS and a predominance of vagal tone, due to depletion of the sympathetic nervous system.

Our study is consistent with the other research findings that have also analyzed HRV in critically ill patients [10-13]. Most of these studies carried out especially in septic patients conclude that those with lower HRV, a decrease in the total energy of the ANS (total power), a reduction of the sympathetic component (LF) and a predominance of the parasympathetic component (HF) presented increased severity according to the APACHE II score and predicted which patients had the highest risk of developing multiple organ dysfunction syndromes (MODS) [12, 13, 18, 19].

Another study by Chen-WL et al. [20] showed that monitoring HRV at the time of admission to the emergency room for patients resuscitated after the myocardial infarction could predict 24-hour mortality. Those with the worst prognosis presented depletion of the sympathetic component (LF) and low autonomic tone (HF), which was very similar to what happened in patients suffering from severe septic shock [13, 21].

Also, Huang CT et al. [14] concluded that spectral analysis of HRV in 101 patients admitted to the intensive care unit undergoing mechanical ventilation could predict the success or failure of removal of said support and that patients extubated with a lower HRV and a lower TP had a higher risk of reintubation after 72 hours. Chen IC et al. [15] demonstrated, as in our study, that lower energy (total power) and higher vagal tone (HF) were independent predictors of mortality in patients with adult respiratory distress syndrome (ARDS).

Finally, a recent meta-analysis of 51 studies [22] that linked HRV and inflammation concluded that spectral analysis serves to monitor the autonomic activity that controls inflammatory processes in humans. In general, these studies have shown a strong association among inflammatory parameters, mainly IL-6 and CRP, and a higher high-frequency band (HF), and a low total power of the ANS, as was also demonstrated in our study.

As Siddiqi HK et al. [4] suggest, there are three stages in the COVID-19 disease. There is the first stage of viral replication, the second stage of lung involvement, with the development of severe pneumonia and ARDS caused by SARS-COV-2 [23], and the third stage with a predominance of a hyper-immune response, with severe multi-organ dysfunction.

What happens in the third stage is severe inflammatory response syndrome (SIRS), extreme macrophage activation, with a significant increase in inflammatory cytokines and other acute-phase reactants (IL-6, ferritin, CRP, D-dimer) [24].

When faced with any infectious or nociceptive stimulus or tissue injury, there is a first proinflammatory response, which is mainly modulated by the sympathetic nervous system [25,26]. This response produces

a strong hyper-immune reaction with a large adrenergic release and significant macrophage activation. This macrophage activation syndrome or SIRS is in turn balanced by a compensatory anti-inflammatory response (CARS). This compensatory response is mostly modulated by the parasympathetic nervous system and by the anti-inflammatory cholinergic pathway. When SIRS subsides and CARS is active for some time, without returning to a state of homeostasis, a state of immunodeficiency or anergy is frequently produced, which triggers an increase in viral replication and bacterial superinfection and can ultimately lead to a fatal outcome for the patient [25-28].

This decreased activity of the ANS, along with the increase in the high-frequency parasympathetic component, seen in patients with COVID-19 and in critically ill patients in general, would represent what happens in the late phase when there is significant autonomic dysregulation, with large-scale sympathetic adrenergic depletion, and a slight predominance of parasympathetic tone as a reflection of the compensatory response [29].

A recent study [30] shows that most of the latest clinical trials on COVID-19 patients have focused primarily on "anti-viral" and "anti-inflammatory" therapeutic strategies. However, it suggests that perhaps a new therapeutic approach for more severely ill patients could be the stimulation of this innate inflammatory response.

There is a nucleus in the brain stem that directs the inflammatory reflex when any injury, infection, or nociceptive stimulus occurs, activating the autonomic nociceptive circuit described by Brown EN et al. [31,32]. This is the nucleus of the solitary tract (NTS), which, through the vagus nerve (VN) and the activation of the different nuclei of the central nervous system, modulates both the sympathetic and parasympathetic nervous systems. The NTS activates the anti-inflammatory cholinergic chain through the VN. The VN is a powerful anti-inflammatory element, as it releases acetylcholine, which inhibits macrophage release of cytokines by binding to its specific membrane receptor, the nicotinic alpha 7 receptor.

In turn, the NTS produces activation of the entire sympathetic chain through the rostral ventromedial medulla (RVM), activates the locus coeruleus (LC) nucleus that regulates the "fight or flight" response through noradrenergic release, and activates the hypothalamic-pituitary-adrenal system by releasing adrenocorticotropic hormone (ACTH) following the activation of the paraventricular (PV) nucleus of the hypothalamus [5,6,26,30].

Therefore, activation of this nucleus, both pharmacologically, by activating the alpha 7 nicotinic receptors, and electrically, through vagus nerve stimulation (VNS), appear to be promising therapeutic strategies to balance the ANS and produce a balanced autonomic response [33-35]. Several studies have already tested VNS in patients with immune system disorders, sepsis and COVID-19 with promising results [36,37], and some clinical trials have started over the last few months [38,39].

This is the first study carried out with certain real-life limitations during the pandemic. Its main limitation is the small sample of patients used. For this reason, further research studies are needed for longer

periods with larger sample sizes. In future studies, we will attempt to monitor and record neuromuscular blocking data using acceleromyograph, and record the degree of sedoanalgesia, using sedation scales and EEG monitors which include spectrogram analysis.

Conclusions

The different components of the spectral analysis of HRV, allow us to infer the state of the autonomic nervous system and the immune system of critically ill patients. Based on the results provided by our study, we can conclude that low autonomic nervous system activity and a predominance of the parasympathetic system due to sympathetic depletion in patients are associated with a worse prognosis and higher mortality. A high ANIm (HFnu) above 80 and a low energy level below 0.41 allows mortality to be predicted with high predictive values.

This autonomic dysregulation likely represents the cause and effect of the different stages of SARS-COV-2 disease, the severe inflammatory system response syndrome, and its compensatory anti-inflammatory response. Therefore, for future studies, we propose that both electrical and pharmacological stimulation of this autonomic nervous system may encourage a balance between the sympathetic/parasympathetic components and might be used as a therapeutic strategy in critically ill patients with COVID-19.

Declarations

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Tables

Table 1
Homogeneity and Comparison of Demographic and Characteristics Data between Groups.

	Survivor Group n = 7	Non - Survivor Group n = 7	p-value
Sex (Male)	4 (57%)	7 (100%)	0.192
Age	64 (60 ; 73)	71 (57 ; 72)	0.797
Weight	74 (68 ; 78)	85 (75 ; 99)	0.085
SOFA	3 (2 ; 6)	8 (3 ; 9)	0.032
RASS	−4 (−4 ;−2)	−5 (−5 ;−4)	0.021
CRP	51 (2.2 ; 197)	112 (26 ; 309)	0.482
IL−6	145 (111 ; 567)	963 (702 ; 1350)	0.055
Procalcitonin	0.6 (0.37 ; 0.65)	0.33 (0.12 ; 0.68)	0.370
Midazolm	3 (43%)	5 (71%)	0.592
Propofol	4 (57%)	1 (14%)	0.266
Dexmedetomidine	2 (29%)	2 (29%)	1.000
Fentanil	2 (29%)	1 (14%)	1.000
Remifentanil	0 (0%)	2 (29%)	0.462
Morphine	3 (43%)	4 (57%)	1.000
Lidocaine	3 (43%)	1 (14%)	0.559
Neuromusc. blockade	1 (14%)	6 (86%)	0.029
Noradrenaline	0/7	3 (43%)	0.192
Dobutamine	1 (14%)	0 (0%)	1.000
Mode (VCV)	3 (43%)	6 (86%)	0.266
FiO2	0.7 (0.7 ; 0.8)	1 (0.8 ; 1)	0.009
Tidal Volume	470 (450 ; 480)	480 (450 ; 520)	0.478
Resp. rate	18 (18 ; 20)	20 (18 ; 20)	0.375

Basic descriptive and tests for the demographic and characteristics variables for each group. Absolute (N) and relative (%) frequencies for the qualitative variables, and median and quartiles (1st ; 3rd) for the quantitative variables. P values were calculated using Mann - Whitney U test. SOFA, Sequential Organ Failure Assessment; RASS, Richmond Agitation-Sedation Scale; CRP, C-reactive protein; IL−6, Interleukin−6; VCV, Volume-controlled ventilation; FiO2, Fraction of inspired oxygen; PEEP, positive end expiratory pressure; PaO2, partial pressure of oxygen in arterial blood; ANIm, mean analgesia nociception index; ANIi, instantaneous analgesia nociception index;

	Survivor Group n = 7	Non - Survivor Group n = 7	p-value
PEEP	8 (6 ; 10)	10 (9 ; 12)	0.032
PaO2	143 (95.6 ; 301)	124 (81.2 ; 137)	0.225
ANIm	64 (53 ; 74)	93 (89 ; 99)	0.003
ANIi	64 (57 ; 76)	94 (87 ; 99)	0.006
Energy	0.57 (0.3 ; 0.63)	0.18 (0.13 ; 0.71)	0.225

Basic descriptive and tests for the demographic and characteristics variables for each group. Absolute (N) and relative (%) frequencies for the qualitative variables, and median and quartiles (1st ; 3rd) for the quantitative variables. P values were calculated using Mann - Whitney U test. SOFA, Sequential Organ Failure Assessment; RASS, Richmond Agitation-Sedation Scale; CRP, C-reactive protein; IL−6, Interleukin−6; VCV, Volume-controlled ventilation; FiO2, Fraction of inspired oxygen; PEEP, positive end expiratory pressure; PaO2, partial pressure of oxygen in arterial blood; ANIm, mean analgesia nociception index; ANIi, instantaneous analgesia nociception index;

Table 2
Sub-analysis for Richmond Agitation-Sedation Scale−4 /−5 patients: Homogeneity and Comparison of Demographic Data and Characteristics between Groups.

	Survivor Group n = 4	Non - Survivor Group n = 7	p-value
Sex (Male)	2 (50%)	7 (100%)	0.109
Age	62 (60 ; 71)	71 (57 ; 72)	0.788
Weight	78 (73 ; 91)	85 (75 ; 99)	0.527
SOFA	2.5 (2 ; 6)	8 (3 ; 9)	0.055
RASS	−4 (−4.75 ;−4)	−5 (−5 ;−4)	0.156
CRP	6.1 (2.2 ; 188.5)	112 (26 ; 309)	0.256
IL−6	153.3 (0.24 ; 1.65)	963 (702 ; 1350)	0.439
Procalcitonin	0.6 (0.24 ; 1.65)	0.33 (0.12 ; 0.68)	0.506
Midazolam	3 (75%)	5 (71%)	1.000
Propofol	1 (25%)	1 (14%)	1.000
Dexmedetomidine	1 (25%)	2 (29%)	1.000
Fentanil	1 (25%)	1 (14%)	1.000
Remifentanil	0 (0%)	2 (29%)	0.491
Morphine	2 (50%)	4 (57%)	1.000
Lidocaine	2 (50%)	1 (14%)	0.491
Neuromusc. blockade	1 (25%)	6 (86%)	0.088
Noradrenaline	0 (0%)	3 (43%)	0.236
Dobutamine	0 (0%)	0 (0%)	1.000
Mode (VCV)	3 (75%)	6 (86%)	1.000
FiO2	0.75 (0.7 ; 0.8)	1 (0.8 ; 1)	0.017
Tidal Volume	480 (420 ; 510)	480 (450 ; 520)	0.848
Resp. rate	18 (16.5 ; 18)	20 (18 ; 20)	0.067

Basic descriptives and tests for the demographic and characteristics variables for each group. Absolute (N) and relative (%) frequencies for the qualitative variables, and median and quartiles (1st ; 3rd) for the quantitative variables. P values were calculated using Mann - Whitney U test. SOFA, Sequential Organ Failure Assessment; RASS, Richmond Agitation-Sedation Scale; CRP, C-reactive protein; IL−6, Interleukin−6; VCV, Volume-controlled ventilation; FiO2, Fraction of inspired oxygen; PEEP, positive end expiratory pressure; PaO2, partial pressure of oxygen in arterial blood; ANIm, mean analgesia nociception index; ANIi, instantaneous analgesia nociception index;

	Survivor Group n = 4	Non - Survivor Group n = 7	p-value
PEEP	9 (7.25 ; 10)	10 (9 ; 12)	0.145
PaO2	265.3 (129.7 ; 309.9)	124 (81.2 ; 137)	0.059
ANIm	61.5 (52.3 ; 73)	93 (89 ; 99)	0.008
ANIi	63 (58.3 ; 79.8)	94 (87 ; 99)	0.014
Energy	0.62 (0.38 ; 0.74)	0.18 (0.13 ; 0.71)	0.186

Basic descriptives and tests for the demographic and characteristics variables for each group. Absolute (N) and relative (%) frequencies for the qualitative variables, and median and quartiles (1st ; 3rd) for the quantitative variables. P values were calculated using Mann - Whitney U test. SOFA, Sequential Organ Failure Assessment; RASS, Richmond Agitation-Sedation Scale; CRP, C-reactive protein; IL−6, Interleukin−6; VCV, Volume-controlled ventilation; FiO2, Fraction of inspired oxygen; PEEP, positive end expiratory pressure; PaO2, partial pressure of oxygen in arterial blood; ANIm, mean analgesia nociception index; ANIi, instantaneous analgesia nociception index;

Figures
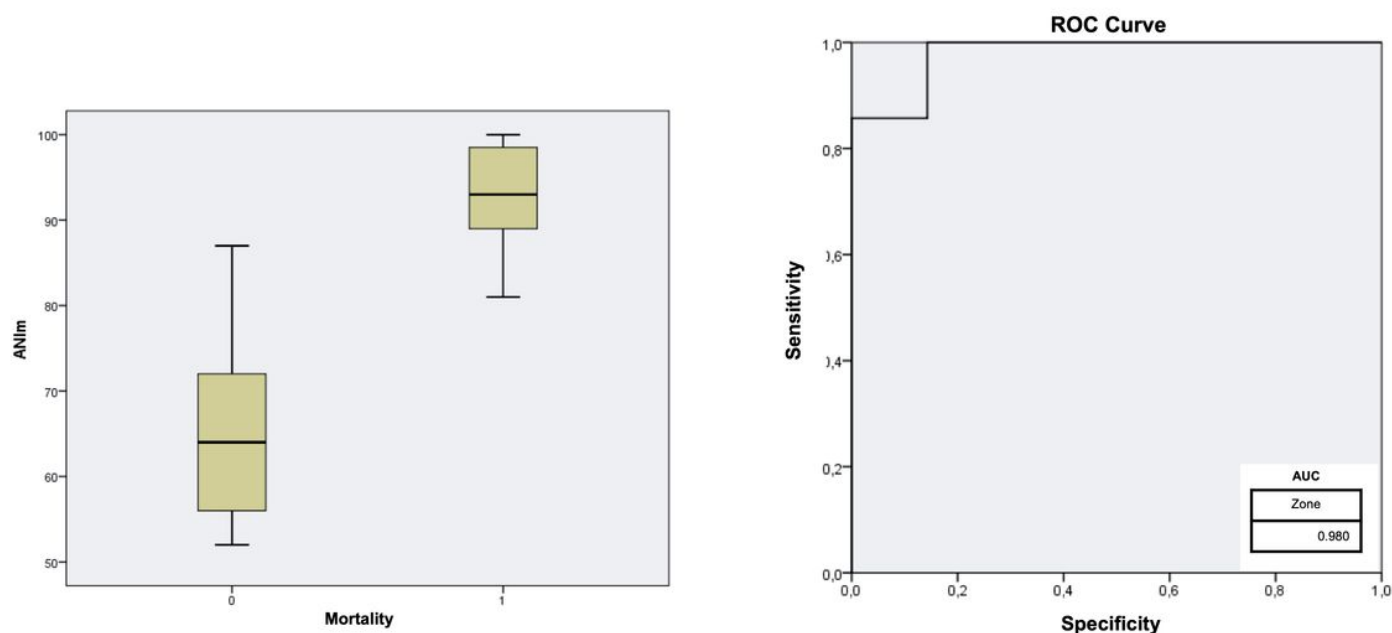
Figure 1

Box Plot (left) and ROC curves for ANIm (right). Box plot represents the median values of ANIm in both groups. ROC curve demonstrates the ability of ANI to discriminate the mortality with an AUC = 0.980 at an ANIm threshold of 80 (sensitivity 100%, specificity 85.7%, a positive predictive value 87.5%, predictive

negative value 100 %). ANIm, median analgesia nociception index; 0 mortality, survivor group; 1 mortality, non-survivor group. AUC, area under the curve;
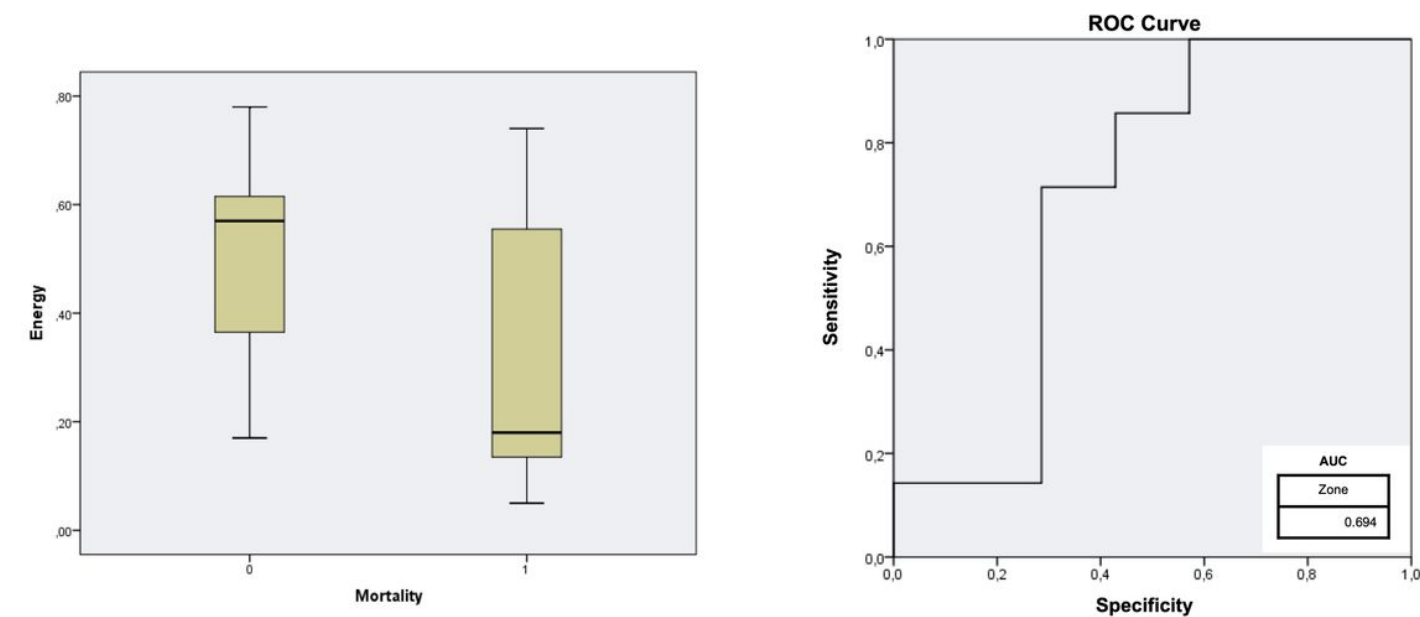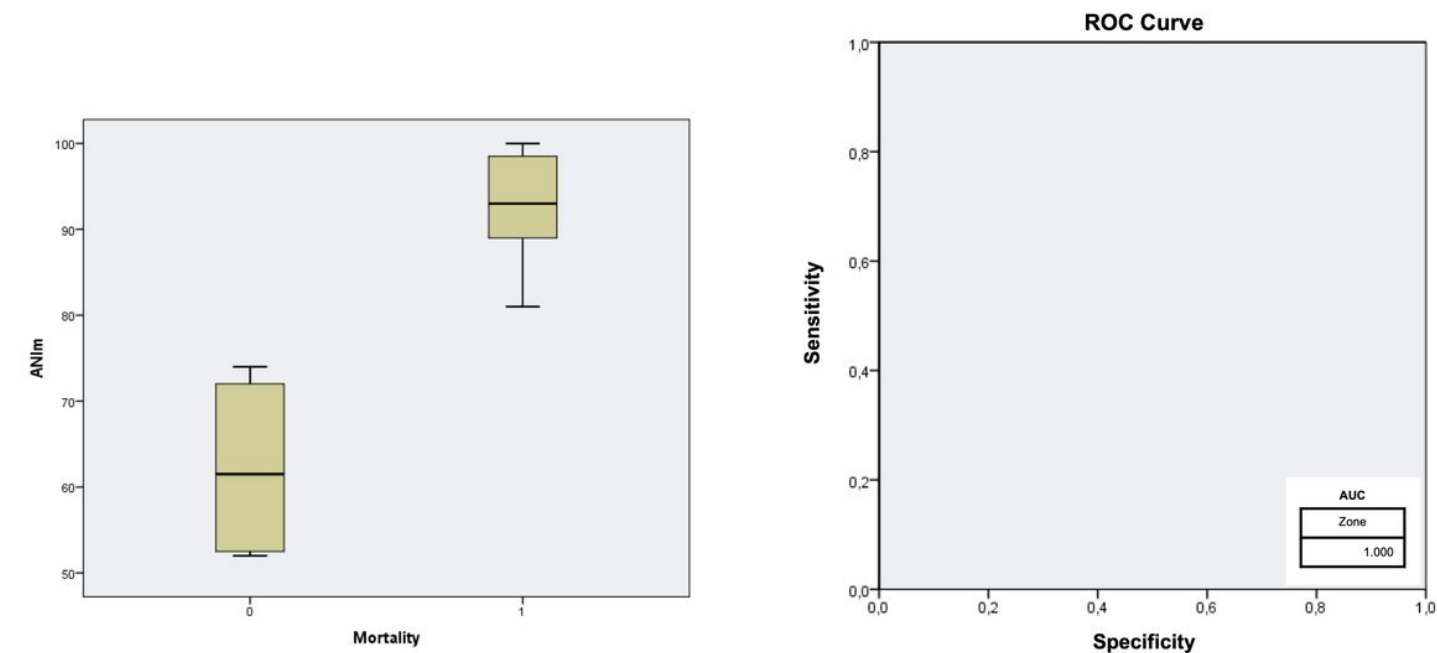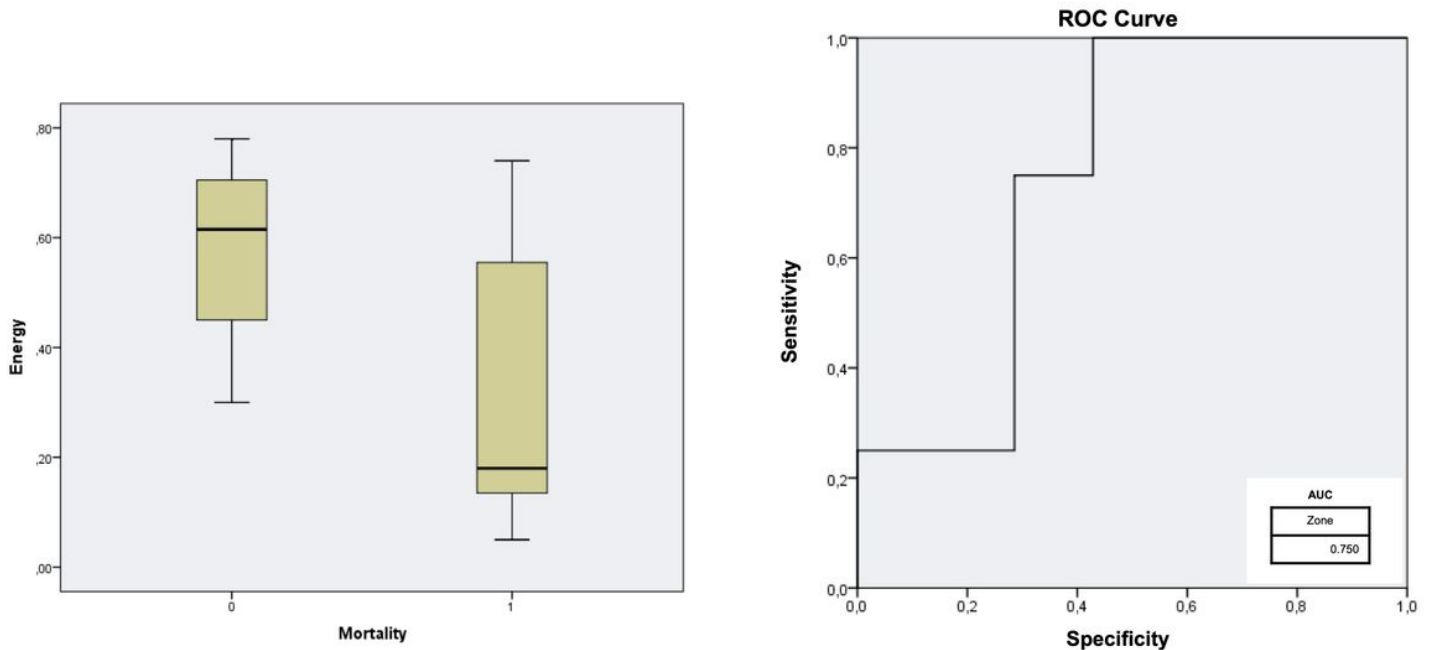

Figure 2

Box Plot (left) and ROC curves for Energy (right). Box plot represents the median values of Energy in both groups. ROC curve demonstrates the ability of Energy to discriminate the mortality with an AUC = 0.694 at a threshold of 0.41 (sensitivity 71.4%, specificity 71.4%, a positive predictive value 71.4%, predictive negative value 71.4%). 0 mortality, survivor group; 1 mortality, non-survivor group. AUC, area under the curve;

Figure 3

Sub-analysis: Box Plot (left) and ROC curves for ANIm (right) in the RASS -4 / -5 patients. Box plot represents the median values of ANIm in both groups. ROC curve demonstrates the ability of ANI to discriminate the mortality with an AUC = 1 at an ANIm threshold of 80 (sensitivity 100%, specificity 100%, a positive predictive value 100%, predictive negative value 100%). ANIm, median analgesia nociception index; 0 mortality, survivor group; 1 mortality, non-survivor group. AUC, area under the curve;

Figure 4

Sub-analysis: Box Plot (left) and ROC curves for Energy (right) in the RASS -4 / -5 patients. Box plot represents the median values of Energy in both groups. ROC curve demonstrates the ability of Energy to discriminate the mortality with an AUC = 0.750 at a threshold of 0.41 (sensitivity 71.4%, specificity 75%, a positive predictive value 83.3%, predictive negative value 60%). 0 mortality, survivor group; 1 mortality, non-survivor group. AUC, area under the curve;