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Laboratorial parameters as predictors of Delirium in elderly subjects hospitalized with acute medical conditions

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Laboratorial parameters as predictors of *Delirium* in elderly subjects hospitalized with acute medical conditions

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ABBREVIATIONS

ADS – American *Delirium* Society;

ALP - Alkaline Phosphatase;

ALT - Alanine Transaminase;

AST - Aspartate Transaminase;

Bl – Day of hospital admission (baseline);

BUN - Blood Urea Nitrogen;

CAM - *Confusion Assessment Method;*

CK - Creatine Kinase;

CNS – Central Nervous System;

Cr – Creatinine;

CRP - C-Reactive Protein;

DSM - *Diagnostic and Statistical Manual of Mental Disorders* (-V;-III-R);

D2 – The second day of hospitalization;

D4 – The fourth day of hospitalization;

EDA – European *Delirium* Association;

Gl - Blood Glucose;

Hb – Hemoglobin;

IGF-1 – Insulin-like Growth Factor - 1;

IL (-1; -6; -8) – Interleukin (-1; -6; -8);

IQR - Interquartile range;

K – Potassium;

Lc – Leukocytes;

LP – Laboratorial Parameters;

MMSE - *Mini-Mental State Examination*;

mRNA – messenger Ribonucleic Acid;

Na – Sodium;

Plt – Platelets;

RASS - *Richmond Agitation-Sedation Scale;*

Tb - Total bilirubin;

TNF-α – Tumor Necrosis Factor - alpha;

γ-GT – Gamma - Glutamyl Transferase;

ABSTRACT

Background: *Delirium* frequently affects acute medically ill elderly patients during hospitalization, and is frequently unrecognized, leading to bad outcomes. Its pathophysiology is poorly understood, whereas laboratorial predictors to be used routinely in clinical settings haven´t been discovered. The aim of this study was to correlate commonly used laboratorial blood parameters (LP) with the presence of *delirium* and to determine whether these tests can predict a *delirium* episode in elderly patients with acute medical conditions.

Methods: The study was prospective and observational, and data were obtained from March to August 2015. We screened 269 elderly male individuals admitted to a general medical ward with acute medical conditions. Participants were assessed on admission (Bl) (n=269), the second day of hospitalization (D2) (n=254), and the fourth day of hospital stay (D4) (n=204). Level of consciousness was assessed with the *Richmond Agitation-Sedation Scale* and presence of *Delirium* with the *Confusion Assessment Method* (confirmed with *Diagnostic and Statistical Manual of Mental Disorders*-V criteria). The most recent LP before each mental status assessment were obtained from clinical records. Statistical analyses were performed as appropriate to determine changes in LP during hospitalization and compare them between patients with and without *delirium* on each of the three assessments. Previous and concomitant LP measures were compared between subjects according to the presence of *delirium* or considerable sedation at D2 and also at D4. Comparisons of LP were also made according to the presence of altered arousal.

Results: On admission, 15,4% of the participants had *delirium*. Leukocytes (Lc), glucose, creatinine, blood urea nitrogen, creatine kinase (CK), and C-reactive protein changed from Bl to D4. During the first half of hospital stay, patients with *delirium* on Bl tended to present

decreasing aspartate transaminase (AST), while *delirium* at D2 was associated with decreasing alkaline phosphatase. Also, these LP varied in narrower ranges than those observed in subjects without *delirium*. Changes in LP during the second half of hospitalization didn´t differ according to the presence of *delirium.* In terms of mean LP, *delirium* was associated with higher AST and Na levels as well as lower Lc, platelet and K values. Also, altered arousal was associated with elevated CK levels.

Discussion and Conclusions: Our study suggests that liver function particularly influences CNS failure during the early stages of altered homeostasis induced by acute illness. We couldn´t find enough evidence to determine commonly used laboratory tests as predictors of a *delirium* episode in acute medically ill subjects.

Key words: *delirium*, consciousness, aging, acute disease, biomarkers.

BACKGROUND

Delirium is a neuropsychiatric syndrome characterized by an acute disturbance of attention and awareness associated with additional cognitive impairment. The symptoms have fluctuations during the course of the day and represent a change in respect to the baseline mental state of the subject.[1] Up to 30% of acute medically ill elderly patients develop *delirium* during hospitalization, while this disorder increases morbidity and mortality rates, prolongs hospital stay, curtails functional recovery, and increments cognitive deterioration.[2] Usually *delirium* is multifactorial in elderly people and results from complex inter-relationships between predisposing and precipitating factors.[3] The leading predisposing factors in medical populations are dementia or cognitive impairment, functional deterioration, visual impairment, history of alcohol misuse, and advanced age.[3] Predominant precipitant factors include acute diseases, metabolic conditions, medications, iatrogenic complications, surgery, trauma and uncontrolled pain.[4] Systemic inflammation is one of the major triggers of *delirium* in elderly and demented subjects, in whom the required inflammatory stimuli is much milder than in healthy populations.[5]

The understanding of *Delirium* pathophysiology is expanding but remains poor due to: difficulties in defining and operationalizing the core features of impaired consciousness and attention; the challenge of recognizing the protean symptoms, severity and evolution; the significant etiological complexity; and the inaccessibility of the central nervous system which limits exploration of the neurobiological correlates of the affected high integrative cognitive functions.[6] Presumably, the synergic interaction among various vulnerability and triggering factors can result in acute failure of several pathways involved in brain homeostasis and induce changes in neuronal activity, affecting the brain´s ability to integrate information.[6] The mechanisms at work can be explained by two hypotheses, the neurotransmitter and the

inflammatory, which probably do not function as separate and distinct entities but rather as complex interplaying processes.[7] While the neurotransmitter hypothesis describes the abundance or deficiency of certain neurotransmitters as the cause for delirious symptoms, the inflammatory hypothesis outlines the similarities between sickness behavior induced by cytokines and *delirium*.[7] It is likely that neuroinflammatory pathways are especially relevant in promoting *delirium* in elderly and demented subjects, considering their increased cerebral vulnerability to the effects of acute systemic inflammation due to primed microglia, increased production of pro-inflammatory mediators, and decreased neuroprotection.[6] Elucidating the pathogenesis of *delirium* could lead to changes in the definition and classification of the syndrome, facilitate recognition and prevention, and also guide the search for biomarkers.

Delirium is a clinical diagnosis frequently unrecognized and easily overlooked.[3] It may be prevented in up to a third of older patients and on that account early recognition is vital.[8] High levels of IL-1, IL-6, IL-8, TNF-α, and S-100β as well as low IGF-1 have been associated with the development of *delirium*, however, most of these parameters are not routinely measured in clinical settings, and some are used only with research purposes.[7] The development of sensitive and specific biomarkers to be used in conjunction with clinical assessment could increase the diagnostic validity of *delirium*, enlighten its pathogenesis, allow preventive strategies, avoid the burden of complications for the patients and also reduce health costs.

The aim of this study is to correlate commonly used laboratorial blood parameters, including measures of inflammation and organ function, with the presence of *delirium* and to determine whether these tests can be used to predict a *delirium* episode in elderly patients with acute medical conditions.

MATERIAL AND METHODS

1. Study Design

An observational prospective study was performed in an Internal Medicine ward of a University Hospital (Centro Hospitalar e Universitário de Coimbra, Portugal).

2. Sample

All male individuals with 65 years or older, admitted to a general medical ward from the 1st of March to the 31st of August 2015, who had an acute medical condition diagnosed were eligible to enter the study. Patients were excluded if their hospital stay lasted less than 48 hours or if they were unable to be assessed due to sensorial deficits, communication problems, or severity of the acute medical condition.

3. Procedures

- ***Delirium*** **diagnosis**

During hospitalization each patient was periodically assessed with the *Richmond Agitation-Sedation Scale* (RASS)[9] for estimation of the level of consciousness and with the *Confusion Assessment Method* (CAM)[10] for the presence of *delirium*. RASS includes four levels of agitation (+1 to +4 [combative]), one level to denote a calm and alert state (0), and five levels of sedation (-1 to -5[unarousable]). Considering that the *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-V[1] criteria for *delirium* imposes that the syndrome doesn´t occur in the context of a severely reduced level of arousal, patients with RASS below -2 were considered too sedated to engage into subsequent cognitive assessment. The remaining patients were screened with CAM for the presence of *delirium* during a brief interview. CAM accesses four cardinal elements of the DSM-III-R criteria for *delirium*: acute onset and fluctuating course (1),

inattention (2), disorganized thinking (3), and altered level of consciousness (4); whereas the presence of features 1 and 2 accompanied by either 3 or 4 is required to establish the diagnosis.[10] Positive cases of *delirium* according to this method were confirmed with DSM-V criteria[1].

Patients were classified in three different ways: in two groups according to the presence of *delirium* during hospitalization; in three groups when patients with moderate or deep sedation (RASS $\leq$ -3) were considered besides subjects with and without *delirium*; and also in two groups setting alert and calm subjects (RASS = 0) apart from agitated or sedated ones (RASS $\neq$ 0).

- **Laboratorial parameters**

The most recent blood analytic parameters before each assessment of RASS and CAM were obtained from clinical records. Laboratorial parameters (LP) of blood count (hemoglobin [Hb], leukocytes [Lc] and platelets [Plt]), blood glucose [Gl], liver function (aspartate transaminase [AST], alanine transaminase [ALT], total bilirubin [Tb], alkaline phosphatase [ALP] and gamma-glutamyl transferase [γ-GT]), renal function (creatinine [Cr] and blood urea nitrogen [BUN]), eletrolytes (sodium [Na] and potassium [K]), creatine kinase [CK], and C-reactive protein [CRP] were studied.

- **Other variables**

Sociodemographic data, chronic comorbidities and the list of regular medications prescribed before hospitalization were obtained from the clinical file. Length of stay was quantified in days.

Each patient was assessed within the first 72 hours of admission by a Psychiatrist. Chronic comorbidity burden was determined using the *Charlson Co-Morbidity scale.*[11]

Functional status on admission was reported in clinical records and rated by the *Barthel Index.*[12] The principal caregiver of each participant was interviewed to evaluate the presence of dementia. This interview was based on the *Informant Questionnaire on Cognitive Decline in the Elderly* (IQCODE-SF)[13], and the caregiver was asked to recollect the situation two weeks before the current admission and compare it with the situation ten years earlier. The diagnosis and severity of dementia were confirmed using operationalized DSM-V[1] criteria and the *Global Deterioration Scale*[14], respectively. Cognitive function was also evaluated with the *Mini-Mental State Examination.*[15]

- **Informed consent**

The procedures and rationale used for the study were explained to all patients and relatives. Because many patients had cognitive impairment, patient assent was always complemented with proxy consent from next of kin or a responsible caregiver, in accordance with the Helsinki Guidelines for medical research involving human participants.[16]

4. Statistical analysis

Presence of *delirium*, level of consciousness, and laboratorial characteristics of each patient were studied on: admission (Bl), the second day of hospitalization (D2), and the fourth day of hospitalization (D4). Statistical analysis was performed using IBM SPSS Statistics 24.0 software (IBM Corp., Released 2013, IBM SPSS Statistics for Windows, Version 24.0., Armonk, NY: IBM Corp.).

Descriptive analysis was used to determine demographic and clinical characteristics of the participants. The Kolmogorov-Smirnov test was applied to assess normality of the variables distribution. Changes in LP from one day to another (Δ1 [Bl to D2] and Δ2 [D2 to D4]) were

investigated using: the Paired Sample T-Test for variables with normal distribution; and the Wilcoxon signed-rank test for variables with non-normal distribution.

Changes in LP ($\Delta 1$ and $\Delta 2$) were compared in two groups of subjects according to the presence of *delirium* on different days of hospitalization. This was analyzed with the Mann-Whitney test, since all variables had non-normal distribution.

Mean LP were compared between three groups of patients: one with *delirium*; one without *delirium; and* another with moderate or deep sedation (RASS $\leq$ -3). LP of Bl and D2 were compared with mental status of D2, while LP of D2 and D4 were compared with mental status of D4. The applied tests were: ANOVA for variables with normal distribution; and Kruskal-Wallis for variables with non-normal distribution.

Mean LP were also compared between a group of alert and calm subjects (RASS = 0) and a group of agitated or sedated patients (RASS $\neq$ 0). LP of Bl and D2 were compared with the level of consciousness of D2, whereas LP of D2 and D4 were compared with the level of consciousness of D4. This analysis was performed with: Independent Sample T-Test for variables with normal distribution; and Mann-Whitney for variables with non-normal distribution.

The level of significance (alpha) was 0.05.

RESULTS

- **Study population and baseline characteristics**

Table 1.Clinical and demographic characteristics of total sample

Mean age[a]		81 ± 7.87
Educational level (school atendance) (%)	**no years of school**	16.4
	1-4 years	71.7
	> 4 years	11.9
Mean Barthel Index[a]		62.97 ± 38.54
Mean Charlson Index[a]		3.16 ± 2.12
Mean MMSE[a]		21.1 ± 7
Dementia (%)		43.5
Mean Global Deterioration Scale[a]		3.56 ± 1.9
RASS at admission (%)	**> 0**	8.2
	0	63.6
	< 0	28.2
***Delirium* at admission (%)**		15.46
Psychotropic drugs prescribed before admission (%)	**Benzodiazepines**	37.5
	Antipsychotics	17.5
	Antidepressants	17.5
Mean Length of stay (days) [a]		11.1 ± 9.39
In-hospital Mortality (%)		9.7

Note. [a]Presented as Mean ± standard deviation.

A total of 335 male subjects were eligible to enter the study. The final sample consisted in 269 participants (Table 1), after excluding those who were unable to undergo cognitive assessment or whose hospital stay lasted less than 48 hours. Patients had a mean age of 81 years and the majority attended school from one to four years. The most prescribed psychotropics were

benzodiazepines. At admission the most frequent level of RASS was the calm and alert state, but still 36.4% of participants had altered arousal. Forty-two subjects were too sedated (RASS ≤ -3) to be assessed for *delirium,* but 15.4% of the remaining patients had this syndrome according to CAM. Formal cognitive assessment with MMSE was not possible at admission in seventy-six patients due to excessive sedation, *delirium,* or dementia severity.

- **Laboratorial parameters at admission and during hospitalization**

All studied LP (table 2) had different means from one day to another, however changes weren´t significant in all tests (table 3). Leukocytes, blood glucose, creatinine, BUN, CK, and CRP had significant changes from Bl to D2 and also from D2 to D4. Sodium, potassium and total bilirubin only changed significantly from Bl to D2, whereas platelets and γ-GT differed significantly from D2 to D4.

Table 2. Laboratorial parameters at admission and during hospitalization

	Baseline (n=269)	**D2** (n=254)	**D4** (n=204)
Leucocytes (G/L)	11.06 ± 5.27	9.65 ± 4.85	10.05 ± 12.34
Platelets (x 10^9/L)	217.67 ± 92.50	221.44 ± 90.11	230.64 ± 95.16
Hb (g/dL)	11.65 ± 2.07	11.54 ± 1.89	11.99 ± 8.99
Na (mEq/L)	137.16 ± 8.98	138.83 ± 5. 88	138.77 ± 5.79
K (mEq/L)	5.04 ± 11.92	4.16 ± 0.51	4.21 ± 0.53
Glucose (mg/dL)	128.56 ± 51.06	118.19 ± 47.16	111.23 ± 42.58
Creatinine (mg/dL)	1.59 ± 2.18	1.40 ± 2.64	1.98 ± 8.96
BUN (mg/dL)	36.95 ± 25.62	33.49 ± 20.81	31.76 ± 20.88
AST (U/L)	41.01 ± 40.49	40.55 ± 53.74	42.75 ± 58.26
ALT (U/L)	35.62 ± 56.07	34.44 ± 47.54	34.94 ± 36.39
ALP (U/L)	144.40 ± 180.74	142.91 ± 179.39	145.23 ± 170.61
γ-GT (U/L)	106.00 ± 190.94	102.36 ± 188.02	112.49 ± 221.44
T bilirubin (mg/dL)	1.39 ± 6.11	0.99 ± 1.43	1.29 ± 3.87
CK (U/L)	211.91 ± 908.67	175.03 ± 694.94	113.51 ± 205.10
CRP (mg/dL)	10.37 ± 10.83	8.23 ± 8.23	6.84 ± 9.83

Note. Presented as Mean ± standard deviation.

Table 3. Changes in mean laboratorial parameters during hospitalization

	Δ1 (D2 – Baseline)		**Δ2 (D4-D2)**	
	n = 254	***p* VALUE[a]**	*n* = 204	***p* VALUE[a]**
Δ Lc	-1.47 ± 3.49	**0.000**[b]	0.19 ± 12.04	**0.013**[b]
Δ Plt	4.11 ± 46.91	0.067[b]	7.21 ± 53.79	**0.005**[b]
Δ Hb	-0.14 ± 1.14	0.059[c]	0.63 ± 8.66	0.647[b]
Δ Na	1.74 ± 7.79	**0.000**[b]	-0.06 ± 3.77	0.853[b]
Δ K	-0.91 ± 12.18	**0.000**[b]	0.05 ± 0.46	0.068[b]
Δ Gl	-10.56 ± 47.73	**0.000**[b]	-6.79 ± 39.67	**0.000**[b]
Δ Cr	-0.18 ± 3.26	**0.000**[b]	0.51 ± 9.30	**0.012**[b]
Δ BUN	-3.26 ± 15.58	**0.002**[b]	-1.78 ± 13.04	**0.009**[b]
Δ AST	0.95 ± 37.69	0.297[b]	0.82 ± 48.47	0.817[b]
Δ ALT	0.32 ± 18.69	0.311[b]	-0.28 ± 30.37	0.094[b]
Δ ALP	-0.11 ± 32.73	0.855[b]	-3.39 ± 59.12	0.334[b]
Δ γ-GT	-1.40 ± 63.15	0.629[b]	7.44 ± 44.79	**0.003**[b]
Δ Tb	-0.42 ± 6.20	**0.034**[b]	0.24 ± 3.48	0.098[b]
Δ CK	-41.11 ± 309.69	**0.000**[b]	-61.87 ± 634.61	**0.000**[b]
Δ CRP	-2.28 ± 10.17	**0.000**[b]	-1.90 ± 9.34	**0.000**[b]

Note. Changes in mean laboratorial parameters from baseline to the second day (Δ1) and from the second to the fourth day (Δ2) of hospitalization.
Presented as Mean ± standard deviation.
[a]Values of $p<0.05$ were statistically significant; [b]With Wilcoxon test for two related samples; [c]With t-test for paired samples.

- **Changes in laboratorial parameters and the presence of *delirium***

Changes from Bl to D2 in mean AST and ALP levels differed significantly in patients with and without *delirium* (table 4.1). A decline in AST levels was more observed in patients with *delirium* than in those without the syndrome at Bl (Fig. 1). Likewise, the presence of *delirium* at D2 was associated with decreasing ALP levels (Fig. 2). Also, global changes of both AST and ALP had narrower ranges in patients with *delirium*.

Table 4.1 Changes in mean laboratorial parameters according to the absence or presence of *delirium*

	Baseline			**D2**		
	No *Delirium* *n* = 178	***Delirium*** *n* = 35	***p* VALUE[a]**	**No *Delirium*** *n* = 188	***Delirium*** *n* = 31	***p* VALUE[a]**
Δ1 Lc	-1.51±3.30	-1.42±3.83	0.335[b]	-1.57±3.45	-2.08±3.69	0.782[b]
Δ1 Plt	8.71±42.01	16.47±38.61	0.443[b]	-0.85±45.34	5.09±36.85	0.542[b]
Δ1 Hb	-0.05±1.17	-0.05±0.80	0.950[b]	-0.11±1.04	-0.17±1.20	0.400[b]
Δ1 Na	1.22±8.63	3.81±6.36	0.058[b]	1.38±8.42	3.58±6.55	0.355[b]
Δ1 K	-0.13±0.57	-0.17±0.58	0.754[b]	-0.16±0.55	-0.20±0.72	0.592[b]
Δ1 Gl	-15.79±44.34	9.06±57.97	0.073[b]	-14.70±46.69	-7.97±34.18	0.952[b]
Δ1 Cr	0.02±3.08	-1.22±5.30	0.949[b]	-0.15±3.73	-0.45±1.54	0.443[b]
Δ1 BUN	-3.57±14.39	-2.08±12.30	0.581[b]	-3.37±13.81	-6.51±24.0	0.733[b]
Δ1 AST	0.83±21.05	6.80±86.55	**0.014**[b]	-0.71±17.42	16.56±91.56	0.593[b]
Δ1 ALT	0.19±19.56	1.49±22.70	0.666[b]	0.05±15.75	4.99±27.75	0.624[b]
Δ1 ALP	1.30±29.93	-2.13±15.68	0.096[b]	-1.07±33.02	-0.76±32.44	**0.013**[b]
Δ1 γ-GT	-4.02±72.89	9.01±39.99	0.770[b]	-3.36±72.33	5.77±24.92	0.732[b]
Δ1 Tb	-0.57±7.40	-0.1±0.37	0.115[b]	-0.54±7.20	-0.07±0.50	0.121[b]
Δ1 CK	-43.2±342.22	-85.05±270.52	0.544[b]	-53.27±341.88	9.91±199.67	0.057[b]
Δ1 CRP	-2.49±11.0	-2.83±6.62	0.853[b]	-2.36±10.81	-2.59±6.22	0.793[b]

Note. Changes in mean laboratorial parameters, from baseline to the second day of hospitalization, according to the absence or presence of *delirium* at baseline and second day in hospital.
Presented as Mean ± standard deviation.
[a]Values of p<0,05 were statistically significant; [b]With Mann-Whitney test.

Changes in mean LP from D2 to D4 were not significantly different according to the presence of *delirium* on D2 or D4 (table 4.2).

Table 4.2 Changes in mean laboratorial parameters according to the absence or presence of *delirium*

	D2			D4		
	No *Delirium* *n* = 148	***Delirium*** *n* = 26	***p* VALUE[a]**	**No *Delirium*** *n* = 151	***Delirium*** *n* = 18	***p* VALUE[a]**
Δ2 Lc	0.59±14.0	-0.42±3.7	0.985[b]	0.57±13.88	-0.52±1.73	0.979[b]
Δ2 Plt	9.83±50.81	0.06±73.67	0.895[b]	9.23±49.61	6.78±38.05	0.329[b]
Δ2 Hb	0.93±10.15	0.03±0.81	0.716[b]	0.88±10.05	0.05±1.29	0.401[b]
Δ2 Na	0.13±2.89	-0.48±5.0	0.472[b]	0.02±3.13	-0.39±4.91	0.783[b]
Δ2 K	0.02±0.44	0.19±0.60	0.123[b]	0.03±0.46	-0.04±0.31	0.529[b]
Δ2 Gl	-5.68±39.11	-9.28±55.26	0.852[b]	-7.69±40.82	-12.27±28.62	0.752[b]
Δ2 Cr	0.52±10.63	-0.09±0.58	0.268[b]	0.71±10.81	-0.05±0.15	0.821[b]
Δ2 BUN	-1.51±10.91	-0.57±19.39	0.696[b]	-2.3±13.02	-2.66±10.94	0.640[b]
Δ2 AST	1.38±47.51	-6.1±46.8	0.352[b]	-0.29±50.32	-2.28±16.75	0.641[b]
Δ2 ALT	0.99±31.72	0.67±13.09	0.355[b]	-0.68±34.47	-1.36±11.67	0.629[b]
Δ2 ALP	-2.75±67.43	-4.58±28.75	0.233[b]	-2.72±67.39	-0.75±10.71	0.671[b]
Δ2 γ-GT	9.84±51.94	1.67±12.21	0.297[b]	10.46±50.46	-4.69±26.14	0.081[b]
Δ2 Tb	0.33±4.08	0.02±0.33	0.548[b]	0.33±4.04	-0.02±0.13	0.535[b]
Δ2 CK	-88.62±735.34	34.31±259.44	0.136[b]	-84.38±726.26	-19.97±101.97	0.959[b]
Δ2 CRP	-1.47±10.11	-3.48±8.05	0.997[b]	-1.68±10.32	-2.21±5.06	0.770[b]

Note. Changes in mean laboratorial parameters, from the second to the fourth day of hospitalization, according to the absence or presence of *delirium* at the second and fourth days in hospital.
Presented as Mean ± standard deviation.
[a]Values of $p<0.05$ were statistically significant; [b]With Mann-Whitney test.

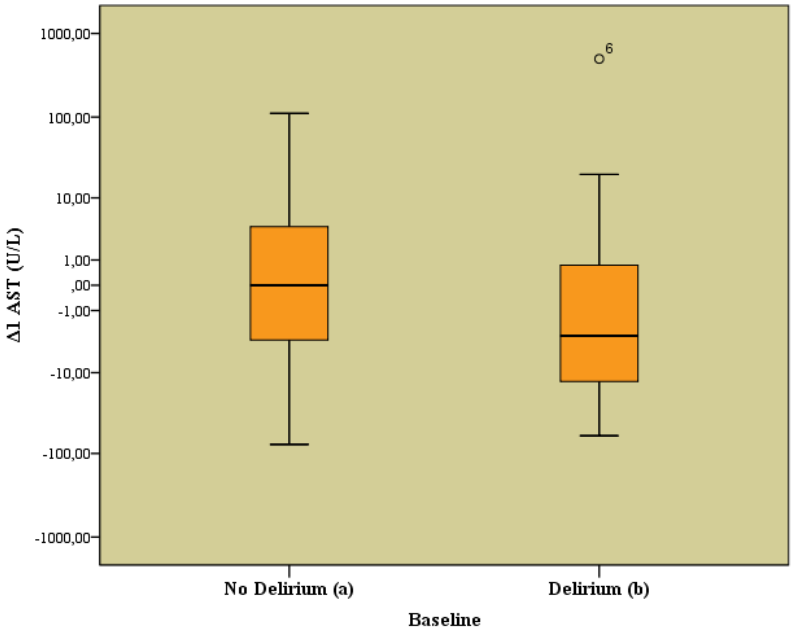

Figure 1. Changes in levels of AST, from Bl to D2, according to the presence of delirium at Bl.

Values of Median[IQR] in:
(a) = 0[-3.6 - 4];
(b) = -3[-13 - 2];

AST values in the graph were log-transformed.

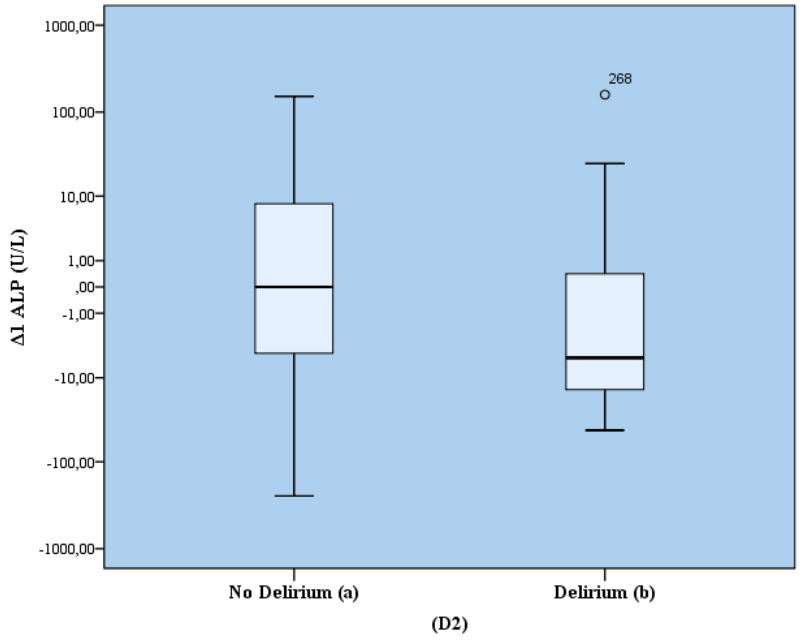

Figure 2. Changes in levels of ALP, from Bl to D2, according to the presence of delirium on D2.

Values of Median[IQR] in:
(a) = 0[-4.9 - 8];
(b) = -5.5[-14 - 1];

ALP values in the graph were log-transformed.

- **Measures of Laboratorial Parameters and the presence of *delirium* or considerable sedation**

Measures of Na, AST, and ALT at Bl differed significantly between patients without *delirium*, with *delirium*, and with considerable sedation (RASS ≤ -3) on D2 (Table 5.1). In patients with *delirium* or considerable sedation, levels of AST were similar and superior to those observed in patients without *delirium*. Values of Na and ALT tended to be higher in patients with moderate or deep sedation than in the other two groups, which presented nearly equal levels of both parameters. Similarly, values of Na at D2 were highest in patients with moderate or deep sedation on D2, however patients with *delirium* showed higher levels than those without the syndrome (Table 5.2).

There was a persistent pattern of differences in leukocytes, platelets, Na and CK measures at D2 (Table 5.3) and D4 (Table 5.4), according the presence of *delirium* and of considerable sedation on D4. Besides, K levels on D4 also presented significant differences between the same three groups of patients (Table 5.4). Leukocytes were higher in patients with moderate or deep sedation, intermediate in patients without *delirium* and lower in patients with *delirium.* In regard to platelet counts, patients with *delirium* had the lowest values, while individuals without *delirium* presented the highest levels (Fig.3-4). Levels of Na were higher in patients with *delirium,* intermediate in patients with moderate or deep sedation, and lower in patients without *delirium* (Fig.5-6). With respect to CK levels, patients with moderate or deep sedation presented the highest values (Fig.7-8). Measures of K on D4 were lower in patients with *delirium*, while similar levels were found between the remaining groups.

Table 5.1 Mean laboratorial parameters according to the presence of *delirium* or considerable sedation during hospitalization

	D2			
	No Delirium *n* = 188	***Delirium*** *n* = 31	**Moderate or deep sedation[c]** *n* = 35	***p* VALUE[a]**
Lc (Bl)	10.99±5.56	11.83±4.53	11.17 ± 4.83	0.332[b]
Plt (Bl)	220.2±94.4	198.7±80.88	218.3±93.1	0.489[b]
Hb (Bl)	11.72±2.15	11.66±1.95	11.45±1.75	0.584[b]
Na (Bl)	136.82±9.58	135.5±7.87	139.5±6.77	**0.028[b]**
K (Bl)	4.33±0.66	4.19±0.79	9.87±33.0	0.170[b]
Gl (Bl)	131.9±55.9	128.3±31.3	112.3±39.0	0.511[b]
Cr (Bl)	1.61±2.38	1.66±1.98	1.35±0.99	0.255[b]
BUN (Bl)	35.75±22.56	38.22±32.49	40.88±27.87	0.631[b]
AST (Bl)	38.07±36.88	43.45±38.97	50.58±52.09	**0.033[b]**
ALT (Bl)	34.23±54.09	26.84±24.99	46.30±73.98	**0.005[b]**
ALP (Bl)	150.7±210.1	124.7±80.2	118.1±59.2	0.212[b]
γ-GT (Bl)	114.9±220.2	71.18±95.55	72.97±61.29	0.066[b]
Tb (Bl)	1.55±7.26	1.25±1.89	0.75±0.46	0.962[b]
CK (Bl)	231.1±1079.6	172.5±226.6	174.2±200.2	0.128[b]
CRP (Bl)	10.13±11.92	12.23±8.83	11.05±6.97	0.171[b]

Note. Mean laboratorial parameters at baseline according to the absence or presence of *delirium*, and to the presence of moderate or deep sedation during the second day of hospitalization.
Presented as Mean ± standard deviation.
[a]Values of $p<0.05$ were statistically significant; [b]With Kruskal-Wallis test; [c]Defined as RASS $\leq$ -3.

Table 5.2 Mean laboratorial parameters according to the presence of *delirium* or considerable sedation during hospitalization

	D2			
	No Delirium *n* = 188	***Delirium*** *n* = 31	**Moderate or deep sedation[d]** *n* = 35	***p* VALUE[a]**
Lc (D2)	9.43±4.96	9.75±4.09	10.77±4.84	0.150[b]
Plt (D2)	225.9±90.4	203.8±99.2	213.2±79.3	0.305[b]
Hb (D2)	11.61±2.02	11.49±1.35	11.2±1.57	0.572[c]
Na (D2)	138.20±5.35	139.08±6.65	142.0±6.89	**0.027[b]**
K (D2)	4.17±0.49	3.99±0.50	4.27±0.57	0.082[b]
Gl (D2)	117.2±47.9	120.3±44.4	121.7±46.6	0.599[b]
Cr (D2)	1.46±3.03	1.21±0.61	1.28±0.88	0.819[b]
BUN (D2)	32.38±19.68	31.70±20.69	41.09±25.42	0.123[b]
AST (D2)	37.36±35.66	60.02±121.10	40.43±34.04	0.187[b]
ALT (D2)	34.28±50.02	31.82±30.57	37.63±47.02	0.326[b]
ALP (D2)	149.6±201.9	123.9±96.4	123.7±76.9	0.719[b]
γ-GT (D2)	111.5±211.5	76.9±113.5	75.7±62.9	0.169[b]
Tb (D2)	1.01±1.39	1.18±2.19	0.69±0.42	0.312[b]
CK (D2)	177.9±798.4	182.4±248.9	153.2±180.5	0.093[b]
CRP (D2)	7.77±7.86	9.63±8.32	9.42±9.92	0.204[b]

Note. Mean laboratorial parameters at second day of hospitalization according to the absence or presence of *delirium*, and to the presence of moderate or deep sedation during the same day. Presented as Mean ± standard deviation.

[a]Values of $p<0.05$ were statistically significant; [b]With Kruskal-Wallis test; [c]With ANOVA test; [d]Defined as RASS ≤ -3.

Table 5.3 Mean laboratorial parameters according to the presence of *delirium* or considerable sedation during hospitalization

	D4			
	No Delirium *n* = 151	***Delirium*** *n* = 18	**Moderate or deep sedation[d]** *n* = 35	***p* VALUE[a]**
Lc (D2)	9.77±5.22	7.25±2.26	9.95±4.46	**0.035[b]**
Plt (D2)	233.02±100.78	172.67±65.91	211.19±67.68	**0.009[b]**
Hb (D2)	11.39±1.85	11.23±1.69	11.29±1.66	0.130[c]
Na (D2)	137.74±5.60	142.0±5.98	140.1±5.90	**0.015[b]**
K (D2)	4.19±0.49	3.96±0.58	4.15±0.57	0.081[b]
Gl (D2)	117.2±45.1	117.9±59.9	121.7±49.7	0.650[b]
Cr (D2)	1.52±3.37	1.22±0.54	1.36±0.92	0.541[b]
BUN (D2)	32.25±19.46	35.06±16.53	38.31±22.59	0.545[b]
AST (D2)	43.19±65.71	33.94±20.64	41.17±35.39	0.572[b]
ALT (D2)	36.81±58.46	27.72±21.80	32.23±21.42	0.131[b]
ALP (D2)	154.0±221.1	130.0±98.0	314.9±94.5	0.952[b]
γ-GT (D2)	112.6±226.4	68.78±101.97	90.96±81.54	0.414[b]
Tb (D2)	1.16±1.81	0.86±0.60	0.69±0.28	0.357[b]
CK (D2)	179.59±877.82	110.89±122.07	180.53±273.1	**0.016[b]**
CRP (D2)	8.54 ±8.34	9.44±7.19	9.29±8.87	0.398[b]

Note. Mean laboratorial parameters at second day according to the absence or presence of *delirium*, and to the presence of moderate or deep sedation during the fourth day of hospitalization. Presented as Mean ± standard deviation.

[a]Values of $p<0.05$ were statistically significant; [b]With Kruskal-Wallis test; [c]With ANOVA test; [d]Defined as RASS ≤ -3.

Table 5.4 Mean laboratorial parameters according to the presence of *delirium* or considerable sedation during hospitalization

	D4			
	No Delirium *n* = 151	***Delirium*** *n* = 18	**Moderate or deep sedation[c]** *n* = 35	***p* VALUE[a]**
Lc (D4)	10.33±14.14	6.73±1.70	10.53±4.26	**0.001[b]**
Plt (D4)	242.25±99.06	179.44±75.42	206.87±73.23	**0.005[b]**
Hb (D4)	12.26±10.39	11.28±1.21	11.13±1.84	0.762[b]
Na (D4)	137.76±5.19	141.61±6.5	141.69±6.48	**0.002[b]**
K (D4)	4.22±0.48	3.92±0.45	4.33±0.72	**0.030[b]**
Gl (D4)	109.5±39.5	105.6±44.13	121.6±53.1	0.126[b]
Cr (D4)	2.23±10.40	1.17±0.56	1.34±1.03	0.864[b]
BUN (D4)	29.95±19.11	32.39±16.03	39.21±28.16	0.162[b]
AST (D4)	42.90±62.65	31.67±16.0	40.23±27.95	0.456[b]
ALT (D4)	36.13±40.49	26.36±14.63	34.19±22.78	0.255[b]
ALP (D4)	151.3±191.6	129.3±94.9	127.3±82.3	0.877[b]
γ-GT (D4)	123.1±252.6	64.08±81.53	91.60±76.50	0.117[b]
Tb (D4)	1.49±4.47	0.84±0.60	0.67±0.20	0.760[b]
CK (D4)	95.20±183.78	90.92±100.92	204.11±298.41	**0.002[b]**
CRP (D4)	6.85±10.82	7.23±6.44	6.61±6.33	0.616[b]

Note. Mean laboratorial parameters at the fourth day of hospitalization according to the absence or presence of *delirium*, and to the presence of moderate or deep sedation during the same day. Presented as Mean ± standard deviation.

[a]Values of $p<0.05$ were statistically significant; [b]With Kruskal-Wallis test;

[c]Defined as RASS ≤ -3.

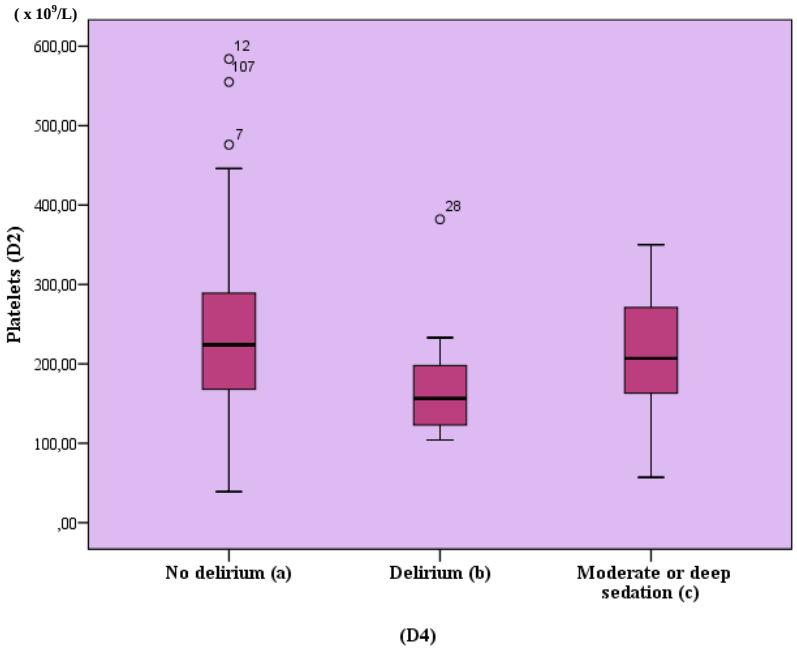

Figure 3. Levels of platelets, on D2, according to the presence of *delirium* and moderate or deep sedation on D4.

Values of Median[IQR] in:
(a) = 224[167-291];
(b) = 156.5[121.8-203];
(c) = 207[162.5-271].

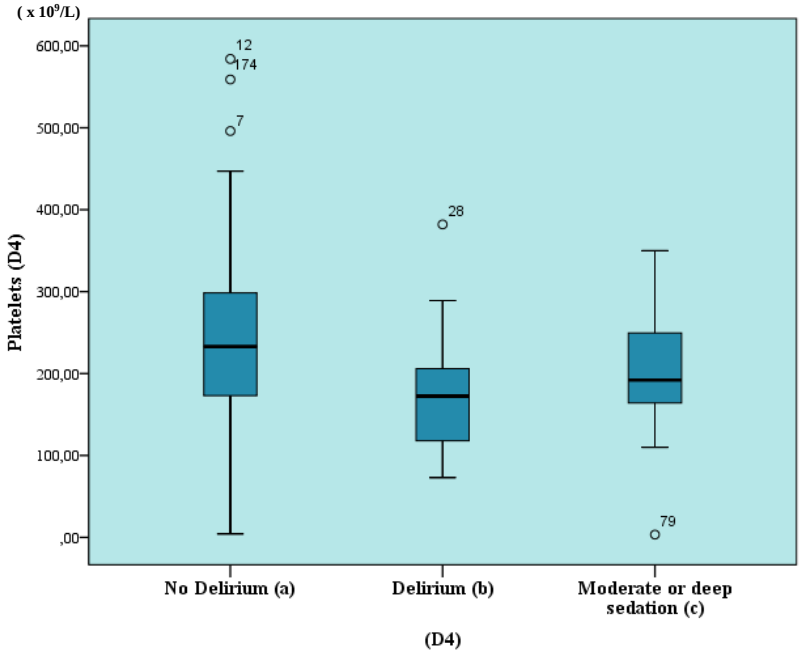

Figure 4. Levels of platelets, on D4, according to the presence of *delirium* and moderate or deep sedation on D4.

Values of Median[IQR] in:
(a) = 233[173-303];
(b) = 172.5[116.8-207];
(c) = 192[164-252].

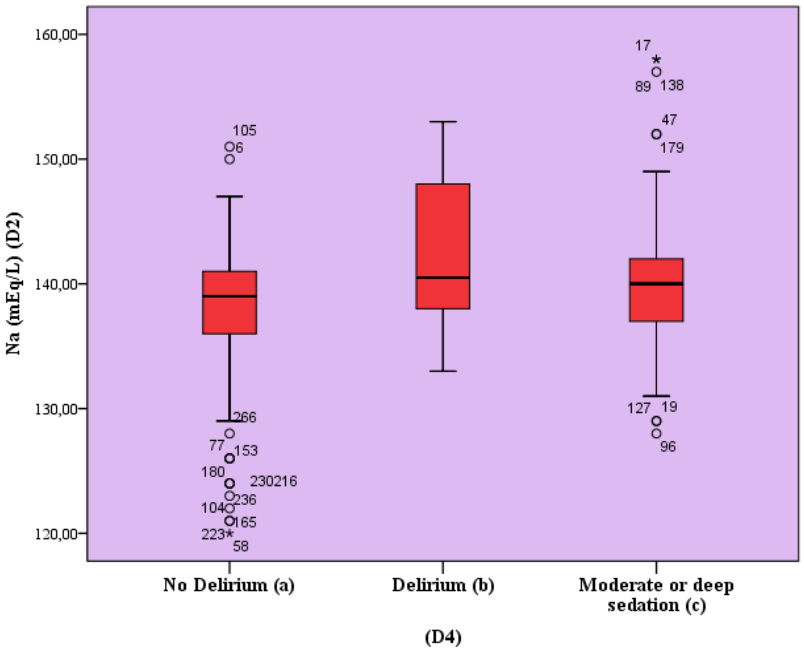

Figure 5. Levels of Na, on D2, according to the presence of *delirium* and moderate or deep sedation on D4.

Values of Median[IQR] in:
(a) = 139[136-141];
(b) = 140.5[137.8-148.3];
(c) = 140[137-142].

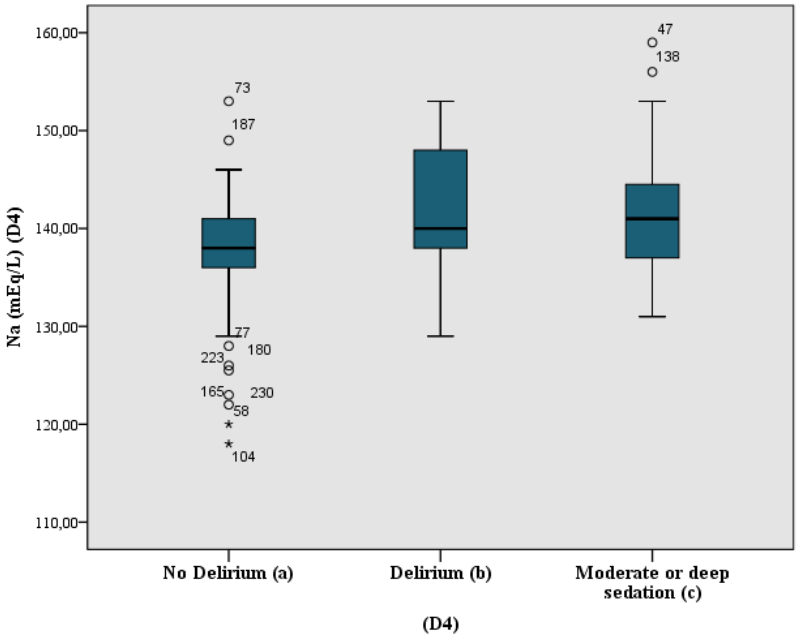

Figure 6. Levels of Na, on D4, according to the presence of *delirium* and moderate or deep sedation on D4.

Values of Median[IQR] in:
(a) = 138[136-141];
(b) = 140[137.8-148.3];
(c) = 141[137-145].

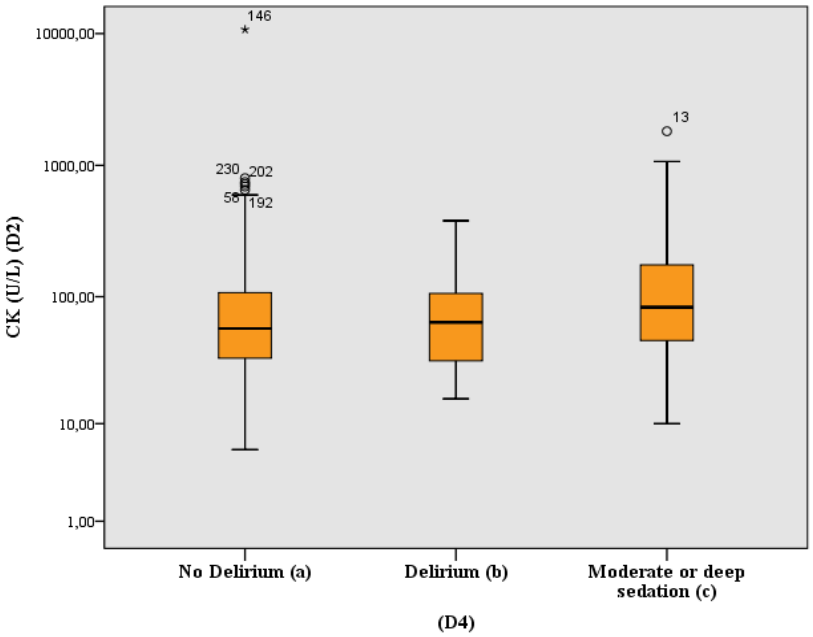

Figure 7. Levels of CK, on D2, according to the presence of *delirium* and moderate or deep sedation on D4.

Values of Median[IQR] in:
(a) = 57[33-108];
(b) = 63.5[31-119.5];
(c) = 83[46-182].

CK values in the graph were log-transformed in.

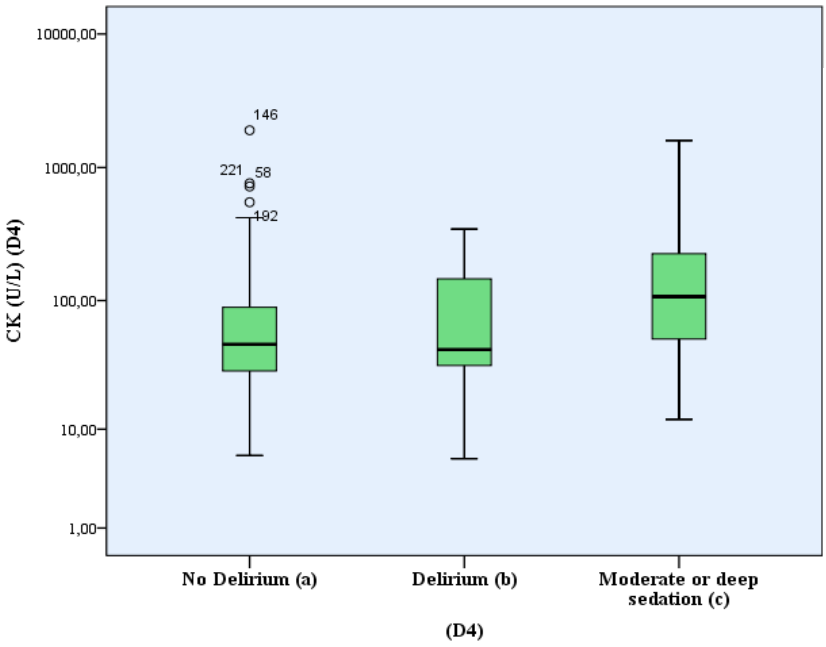

Figure 8. Levels of CK, on D4, according to the presence of *delirium* and moderate or deep sedation on D4.

Values of Median[IQR] in:
(a) = 46.5[29-89];
(b) = 42.5[30.3-149];
(c) = 107[51-253].

CK values in the graph were log-transformed.

- **Laboratorial parameters and the presence of altered arousal**

Table 6. 1 Mean laboratorial parameters according to the presence of altered arousal during hospitalization

	D2						
	Alert and calm[d] *n* = 171	**Agitated or sedated[e]** *n* = 83	***p* VALUE[a]**		**Alert and calm[d]** *n* = 171	**Agitated or sedated[e]** *n* = 83	***p* VALUE[a]**
Lc (Bl)	11.14±5.77	11.07±4.36	0.440[b]	**Lc (D2)**	9.38±5.09	10.20±4.28	**0.036[b]**
Plt (Bl)	220.13±95.75	211.54±86.06	0.561[b]	**Plt (D2)**	228.35±94.0	207.19±80.1	0.115[b]
Hb (Bl)	11.66±2.13	11.71±1.94	0.862[c]	**Hb (D2)**	11.59±2.02	11.45±1.61	0.869[b]
Na (Bl)	136.79±9.59	137.70±8.34	0.294[b]	**Na (D2)**	138.33 ±4.87	139.86±7.46	0.190[b]
K (Bl)	4.28±0.66	6.70±21.43	0.557[b]	**K (D2)**	4.17±0.48	4.16±0.55	0.596[b]
Gl (Bl)	134.89±58.08	116.11±32.16	0.145[b]	**Gl (D2)**	120.76 ±51.32	112.89±36.85	0.516[b]
Cr (Bl)	1.48±1.07	1.78±3.51	0.211[b]	**Cr (D2)**	1.48±3.17	1.25±0.77	0.435[b]
BUN (Bl)	35.97±24.07	38.38±25.95	0.546[b]	**BUN (D2)**	31.89±19.06	36.8±23.82	0.186[b]
AST (Bl)	39.12±38.96	40.57±33.99	0.168[b]	**AST (D2)**	41.46±61.57	38.66±32.36	0.144[b]
ALT (Bl)	36.04 ±56.39	30.15±41.94	0.818[b]	**ALT (D2)**	36.57 ±52.7	30.06±34.48	0.623[b]
ALP (Bl)	151.42±215.86	125.70±89.36	0.755[b]	**ALP (D2)**	150.91±210.0	126.42±86.3	0.969[b]
γ-GT (Bl)	120.36±230.10	69.57±71.28	0.340[b]	**γ-GT (D2)**	116.89±222.0	72.44±74.43	0.264[b]
Tb (Bl)	1.64±7.61	0.91±1.22	0.123[b]	**Tb (D2)**	1.05 ±1.45	0.88±1.38	0.135[b]
CK (Bl)	231.16±1127.2	185.21±245.1	0.252[b]	**CK (D2)**	174.66±833.89	175.80±219.96	**0.001[b]**
CRP (Bl)	11.03±12.46	9.44±7.12	0.735[b]	**CRP (D2)**	8.13 ±8.04	8.43±8.64	0.681[b]

Note. Mean laboratorial parameters, at baseline and second day, according to the presence of altered arousal during the second day of hospitalization.

Presented as Mean ± standard deviation.

[a]Values of $p<0.05$ were statistically significant; [b]With Mann-Whitney test; [d]With Independent Sample T-Test; [d]Defined as RASS = 0; [e]Defined as RASS ≠ 0.

Table 6. 2 Mean laboratorial parameters according to the presence of altered arousal during hospitalization

	D4						
	Alert and calm[d] *n* = 137	**Agitated or sedated[e]** *n* = 67	***p* VALUE[a]**		**Alert and calm[d]** *n* = 137	**Agitated or sedated[e]** *n* = 67	***p* VALUE[a]**
Lc (D2)	9.63±5.20	10.34±4.83	0.203[b]	**Lc (D4)**	8.99±4.31	12.20±20.56	0.191[b]
Plt (D2)	232.8±102.3	204.3±74.1	0.054[b]	**Plt (D4)**	245.65±98.6	199.95±79.97	**0.002[b]**
Hb (D2)	11.36±1.85	11.37±1.69	0.968[c]	**Hb (D4)**	11.47±1.93	13.04±15.46	0.600[b]
Na (D2)	137.75±5.29	141.05±7.38	**0.002[b]**	**Na (D4)**	137.78±5.13	140.79±6.54	**0.005[b]**
K (D2)	4.19±0.47	4.10±0.59	0.168[b]	**K (D4)**	4.22±0.48	4.21±0.63	0.628[b]
Gl (D2)	115.77±44.71	122.62±51.74	0.544[b]	**Gl (D4)**	109.3±40.6	115.1±46.4	0.548[b]
Cr (D2)	1.56±3.53	1.28±0.76	0.661[b]	**Cr (D4)**	2.35±10.92	1.23±0.83	0.287[b]
BUN (D2)	32.38±19.98	35.89±19.49	0.141[b]	**BUN (D4)**	30.16±19.9	35.02±22.7	0.073[b]
AST (D2)	45.70±68.73	34.54±27.76	0.951[b]	**AST (D4)**	44.81±65.39	34.59±23.17	0.652[b]
ALT (D2)	39.58±61.15	26.31±18.07	0.778[b]	**ALT (D4)**	38.83±41.89	26.98±19.02	0.187[b]
ALP (D2)	158.9±231.1	127.6±87.5	0.787[b]	**ALP (D4)**	155.1±199.9	125.1±81.13	0.966[b]
γ-GT (D2)	118.62±236.2	77.32±84.33	0.630[b]	**γ-GT (D4)**	128.6±263.6	79.5±77.20	0.684[b]
Tb (D2)	1.20±1.89	0.75±0.42	0.206[b]	**Tb (D4)**	1.57±4.69	0.73±0.40	0.434[b]
CK (D2)	182.54±919.6	160.75±192.35	**0.021[b]**	**CK (D4)**	95.41±187.7	150.51±236.3	**0.032[b]**
CRP (D2)	8.33±8.24	9.61±8.45	0.184[b]	**CRP (D4)**	6.71±11.12	7.11±6.51	0.164[b]

Note. Mean laboratorial parameters, at second and fourth days, according to the presence of altered arousal during the fourth day of hospitalization.

Presented as Mean ± standard deviation.

[a]Values of $p<0.05$ were statistically significant; [b]With Mann-Whitney test; [c]With Independent Sample T-Test; [d]Defined as RASS = 0; [e]Defined as RASS $\neq 0$.

Measures of leukocytes and CK at D2 differed significantly between patients with and without altered arousal (RASS ≠ 0 or = 0) on D2 (Table 6.1). Subjects agitated or sedated tended to present higher levels of leukocytes (Fig. 9).

Patients with a state of agitation or sedation on D2 presented higher CK levels at D2 (Fig. 10). Likewise, altered arousal on D4 was associated with higher CK values at D2 and D4 (Table 6.2; Fig. 11-12).

Besides CK, values of platelets and Na also differed significantly according to the level of arousal on D4 (Table 6.2). Agitated or sedated patients presented lower platelet counts at D4 (Fig. 13), and higher levels of Na at D2 and D4.

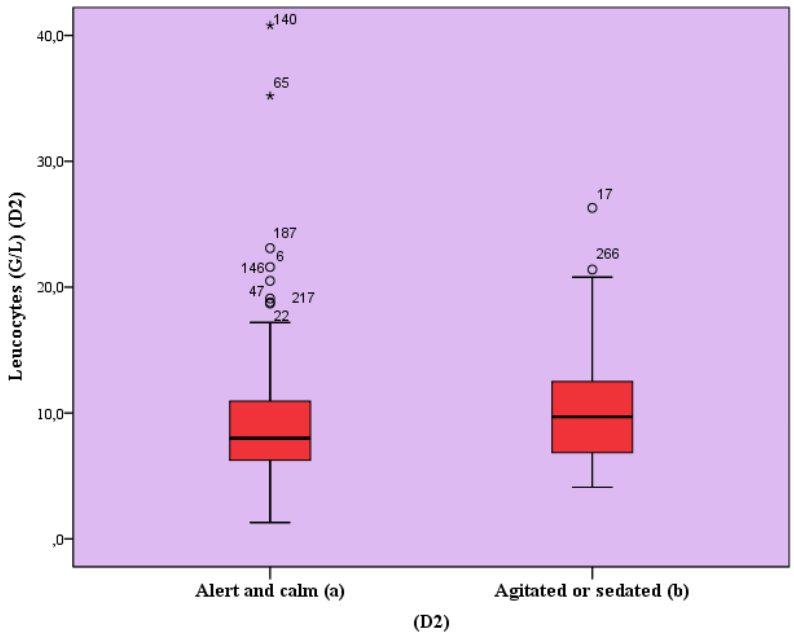

Figure 9. Levels of Leukocytes, on D2, according to the level of arousal on D2.

Values of Median[IQR] in:
(a) = 8[6.2-11];
(b) = 9.7[6.8-12.5];

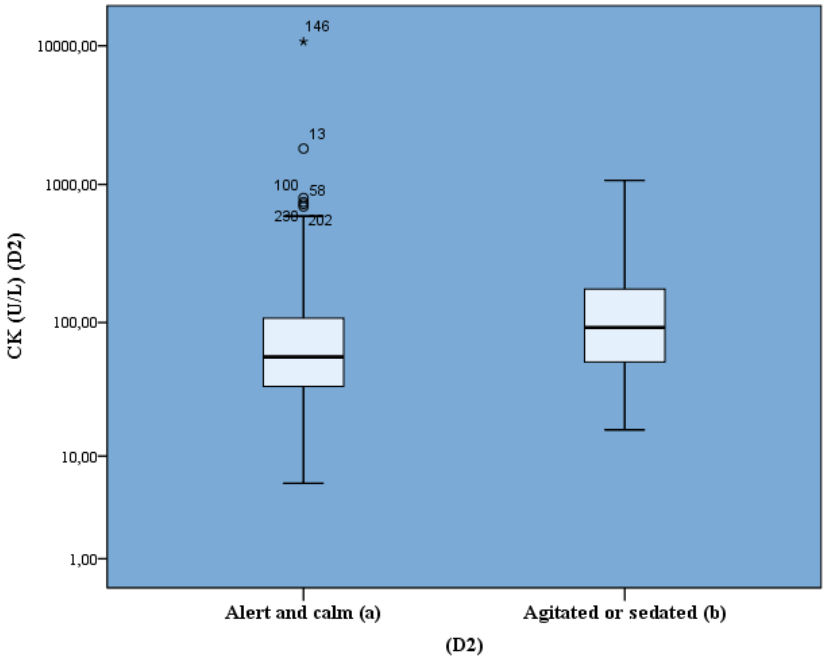

Figure 10. Levels of CK, on D2, according to the level of arousal on D2.

Values of Median[IQR] in:
(a) = 56[34-108];
(b) = 92[51-175];

CK values in the graph were log-transformed.

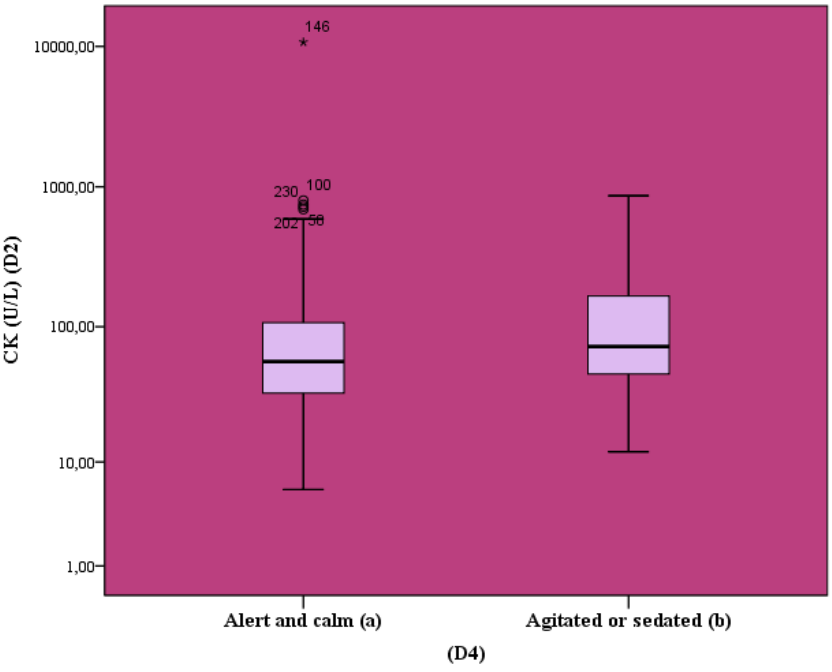

Figure 11. Levels of CK, on D2, according to the level of arousal on D4.

Values of Median[IQR] in:
(a) = 56[32.5-107];
(b) = 72[45-172];

CK values in the graph were log-transformed.

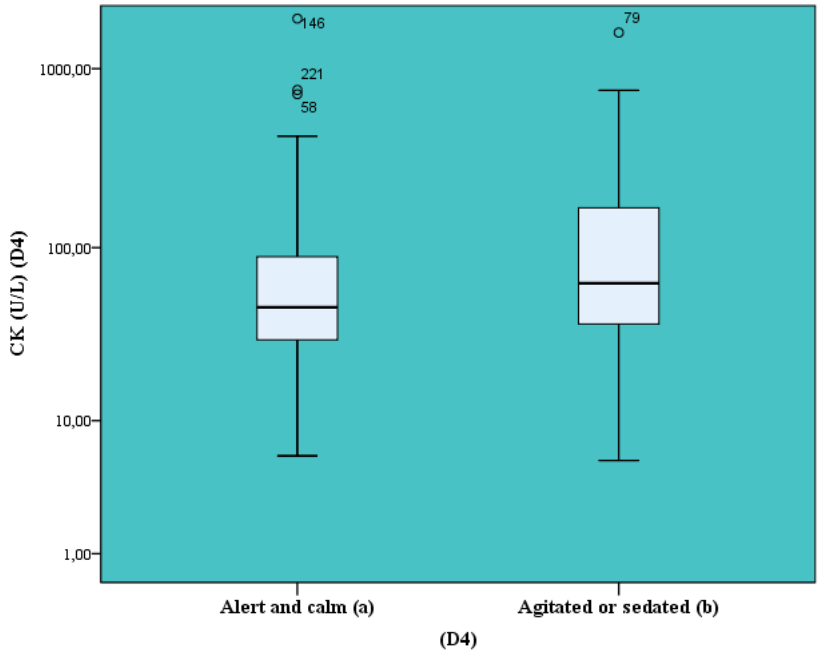

Figure 12. Levels of CK, on D4, according to the level of arousal on D4.

Values of Median[IQR] in:
(a) = 46[29.5-89];
(b) = 63[36-173];

CK values in the graph were log-transformed.

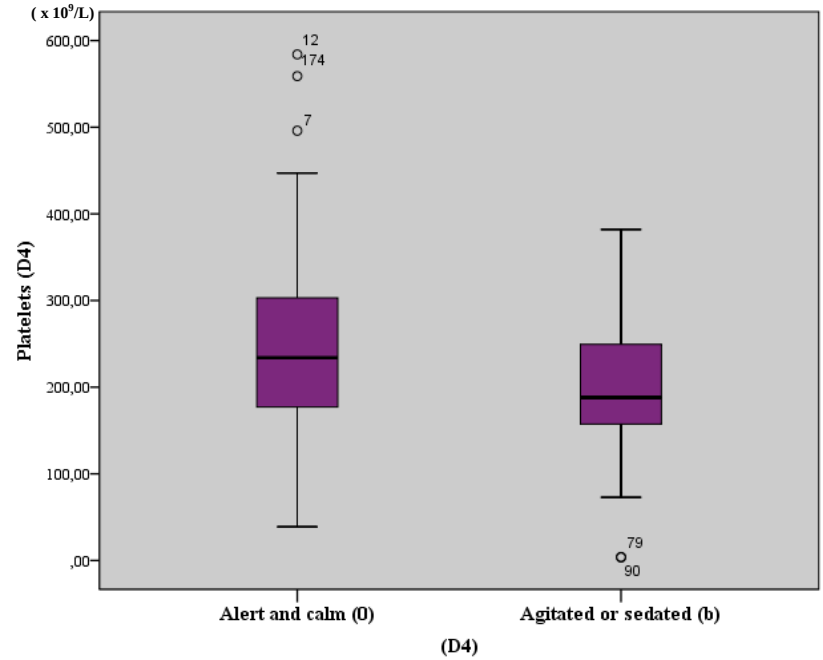

Figure 13. Levels of Platelets, on D4, according to the level of arousal on D4.

Values of Median[IQR] in:
(a) = 234[175.5-308];
(b) = 188[155-252];

DISCUSSION

Delirium is a result of acute CNS failure as different pathophysiological processes converge into common pathways that ultimately lead to the impairment of high integrative cognitive functions.[6] In this study we determined if laboratorial blood parameters, including measures of inflammation and organ function, can be used to predict a *delirium* episode in elderly patients with acute medical conditions.

In this series, accordingly with other studies[8], *delirium* was present in 15.46% of the patients at admission, and in-hospital mortality was of 9.7%.

To our knowledge the association between variations in LP during hospitalization and the presence of *delirium* has not been assessed. Other researchers studied measures of LP observed at a certain moment before or after the onset of *delirium*. Besides, most studies analyzed critically ill or surgical patients. Despite this, it has been determined that elevated leukocytes, BUN, AST, and CRP levels as well as decreased K levels were independent risk factors for *delirium* in patients with acute and subacute diseases.[17] In the emergency department of a Portuguese hospital, delirious patients had higher BUN, creatinine and osmolarity as well as lower hemoglobin levels, when compared to subjects without *delirium*.[18] Also, in a surgical intensive care unit, anemia, hyponatremia, high BUN, elevated liver enzymes and hyperbilirubinemia were identified as predictors of *delirium*.[19]

Sequential assessments during hospitalization revealed significant changes in some LP reflecting a diversity of physiological reactions to regain homeostasis following an acute medical condition. According to its nature, CRP levels decreased progressively since the acute phase of inflammatory response.[20] Leukocyte counts decreased, likely due to recovery from infection, but slightly increased later which could consist in restitution of reserves after intense turnover during

response to aggression. Na increased until D2 probably reflecting dehydration. Recovering from kidney injury could explain the initial decrease in creatinine and BUN[20], however, creatinine increased later, possibly reflecting further renal damage. K levels decreased until D2 perhaps due to correction of acidosis or renal loss.[20] Glycemia decreased progressively but was elevated at Bl which could be due to cortisol effects as a stress response.[20] CK decreased persistently and might have increased previously due to muscular or cardiac stress, which can both be caused by infection.[20] γ-GT increased since D2 and this could be due to hepatobiliary injury or drug toxicity.[21]

It should be noted that elderly patients have accumulated deficiencies and reduced thresholds for coping with stress, making them vulnerable to the effect of acute medical conditions and their disturbances in homeostasis.[22]

Some changes in LP differed significantly in patients with and without *delirium.*

During the first two days of hospitalization, patients with *delirium* at Bl had more tendency to present decreasing values of AST than patients without the syndrome. In the same period, patients with *delirium* at D2 more commonly presented decreasing values of ALP. Also, global changes of both AST and ALP had narrower ranges in patients with *delirium*. This suggests that hepatic metabolism could have influence in *delirium* trough an unknown mechanism.

The systemic acute inflammatory response causes early liver reactions with uptake of amino acids, iron and zinc, as well as changes in hepatocyte mRNA to allow increased secretion of plasma acute phase proteins, including fibrinogen and CRP.[23] This response induces hepatic enzyme activity[20] and different patterns of that activity in delirious patients could be related with the occurrence of particular reactions to acute illness in *delirium*. Also, evidence suggests that

delirium is caused by several different sets of interacting biological factors[3], whereas various bioactive substances have hepatic synthesis, secretion and excretion.[20] Thus liver function influences several physiological factors that can potentially interact and result in *delirium*.

Changes in LP during the second half of hospitalization had no significant differences according to the presence of *delirium,* suggesting that a possible influence of hepatic metabolism in this syndrome would occur in early stages.

Analyzing measures of LP, some parameters differed between patients without delirium, with *delirium,* and with considerable sedation. The LP that differed according to the presence of *delirium* were AST, Na, platelets, leukocytes and K. These could possibly contribute to *delirium* prediction if included in a tool to systematically assess vulnerability in elderly patients with acute medical conditions. The use of these parameters simultaneously reflects different biological pathways and could better identify patients at risk than each LP *per se,* since *delirium* is likely caused by different sets of predisposing and precipitating factors.

Measures of AST at Bl differed according to the presence of *delirium* or of considerable sedation on D2. Levels of AST were similar between delirious and considerably sedated patients, and these values were superior to those observed in subjects without *delirium*. Accordingly, a study evidenced higher AST levels in delirious surgical patients than in those without the syndrome.[17]

Elevated AST could be due to hepatitis, cirrhosis, and hepatic failure, all conditions commonly associated with *delirium*[6]. Besides, hepatic encephalopathy can be a contributing factor in subjects with liver dysfunction and *delirium.*[24] On the other hand, AST could be linked

to *delirium* in patients without liver dysfunction, since this enzyme can be elevated due to congestive heart failure or myocyte injury.[21]

Platelet counts at D2 and D4 varied according to the presence of *delirium* or of considerable sedation on D4. Considering both measures, the lowest platelet values were associated with *delirium*, whereas the highest levels corresponded to the absence of the syndrome. These results are in agreement with other studies[17,25], but it has been discussed that a significant decrease in platelets is not equivalent to thrombocytopenia in patients with *delirium*, possibly being a consequence of anemia or infection[17]. It is described that platelet counts begin to fall at the age of 60 years old and that they undergo changes during ageing, while their function is also influenced by commonly used treatments such as anti-platelet drugs, statins and, nitrates.[26] Despite this understanding, our results suggest that platelets are decreased in *delirium*.

There was a common pattern of differences in measures of Na, at D2 and D4, according the presence of *delirium* or of considerable sedation on D4. The highest Na levels occurred in patients with *delirium*, whereas the lowest ones were found in patients without the disorder. Ahmed et al. reviewed that high or low Na levels have been some of the LP most commonly associated with *delirium* among older people in acute hospital medical units.[8] Contrarily to our results, other studies found association between hyponatremia and *delirium*[19] or no association between Na levels and the syndrome at all[17].

Hypernatremia is more commonly caused by water deficiency due to inadequate intake.[27] Elderly ill subjects are at increased risk of dehydration[27] which is a known risk factor for *delirium*.[28] And while some studies revealed that loss of 2% of total body water causes impairment in visuospatial processing, short-term memory, and attention, it is hypothesized that

dehydration causes neuronal death, cytokine and nitrous oxide release, and neurotransmitter dysfunction.[29] Thus, our results support a relation between *delirium* and water deficit, whereas events associated with acute illness such as fever, vomiting, and diarrhea, might have contributed to fluid loss.

There was a persistent pattern of Leukocyte counts, at D2 and D4, according the presence of *delirium* or considerable sedation on D4. Patients with *delirium* presented the lowest leukocyte counts, while considerably sedated subjects had the highest values. Contrarily, other studies have associated increased white blood cells[17] with *delirium*, but they studied LP findings previous to the diagnosis. Prominent systemic inflammatory reactions are implicated in *delirium*, while this syndrome is a common manifestation of septic multiorganic dysfunction and of underlying urinary tract infection or pneumonia.[6] Our finding of lower leukocytes in delirious patients could be due to immunosuppression caused by an exaggerated inflammatory state, similarly to what occurs in sepsis[30].

Measures of K on D4 varied according to the presence of *delirium* or considerable sedation on the same day. In agreement with other studies[17], patients with *delirium* had lower K concentrations than the remaining groups. Besides, abnormal K is described as a precipitating factor in surgical non-cardiac settings.[3]

Numerous subjects were too sedated (RASS $\leq$ -3) to be assessed for *delirium* in the current study. When diagnosing *delirium* acordding to DSM-V[1] criteria, the EDA and ADS recommend that patients who are not comatose, but have impaired arousal precluding cognitive assessment, must be understood as effectively having inattention, whereas considering such patients as having *delirium* agrees with the scientific evidence and increases patients

safety.[31]Accordingly, a study showed that a RASS score ≠ 0 had very good sensitivity and specificity for diagnosing *delirium* in older emergency department patients.[32] Following the notion that impaired arousal is part of the *delirium* spectrum, we analyzed measures of LP according to the presence of sedation or agitation in order to ascertain if the observed patterns would be similar to those in *delirium*. And as occurred in *delirium*, altered arousal was associated with higher Na and lower platelet levels.

Interestingly, CK differed significantly between patients with and without altered arousal but not between subjects with and without *delirium*. Patients who were agitated or sedated on D2 had concomitant higher CK levels than calm and alert subjects. Likewise, altered arousal on D4 was associated with higher values of CK at both D2 and D4. And it has been suggested that agitation is determinant for CK elevation in psychotic patients.[33]As CK is mainly found in the skeletal muscles, heart and brain, its elevation usually indicates damage or stress in any of these organs. [33]

This study comprehends certain limitations. Although the sample size provided adequate statistical power to identify correlations between LP and *delirium* symptoms, a larger sample would be more representative of delirious elderly patients presenting with acute medical conditions. Also, further work should replicate these investigations elsewhere as this study was implemented in a single hospital, even though it is likely to be illustrative of medical settings in general.

Some limitations warrant cautious interpretation of these results. Important factors influencing LP, such as nutritional status, complete medication and specific causes of admission were not assessed in the current study. Also, the obtained LP values do not necessarily reflect the

dynamic variations of each analyzed parameter between blood collections. Moreover, although cases of *delirium* were confirmed according to DSM-V criteria, important clinical features, including motor subtypes, the duration of full-blown *delirium,* and persistence of subsyndromal symptoms were not considered.

CONCLUSIONS

This study suggests that liver function particularly influences CNS failure during altered homeostasis induced by acute illness.

Hepatic encephalopathy provides an example of a synergism between ammonia and inflammation contributing to *brain failure,*[34] possibly illustrating the impact of liver function in the CNS. In this disorder, hepatic nitrogen metabolism is decreased and ammonia accumulates in systemic circulation, crosses the blood-brain barrier, and possibly causes edema of brain cells and increased γ-aminobutyric acid activity.[24] Peripheral inflammation is thought to exacerbate neurological compromise, acting in synergy with ammonia to change cerebrovascular hemodynamics, produce pro-inflammatory mediators, and deregulate immune activity.[34] Inflammation can also arise within the brain, as a result of deranged nitrogen and energy homeostasis, leading to astrocytic, microglial, and neuronal dysfunction.[34] Further studies involving these pathways could contribute to understanding the weight of liver function in *delirium*.

We couldn´t find enough evidence to determine commonly used laboratory tests as predictors of a *delirium* episode in acute medically ill subjects.

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