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# *PREVENTING DELIRIUM: IDENTIFICATION OF RISK GROUPS IN ELDERLY PATIENTS WITH ACUTE MEDICAL CONDITION*

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# Preventing *Delirium*: identification of risk groups in elderly patients with acute medical condition

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## Abstract

**Background:** *Delirium* is a frequent neuropsychiatric syndrome associated with serious outcomes affecting mainly elderly subjects with acute medical disorders. Although it is widely accepted that *delirium* is the result of an interplay between predisposing and precipitating factors, the specific role of a particular risk factor remains largely unknown. Exploring how the etiological factors interact with each other can facilitate the early diagnosis of *delirium* and clarify the pathophysiological mechanisms involved in this condition.

**Objectives:** Explore how risk factors of *delirium* co-occur in medically-ill elderly patients with this syndrome and identify sub-groups of those risk factors.

**Materials and Methods:** Sociodemographic characteristics, acute medical conditions and chronic medical comorbidities were characterized in a group of 82 acutely-ill medical elderly patients diagnosed with *delirium* (CAM and DSM-IV-TR). A hierarchical cluster analysis of all risk factors was carried out using SPSS 22.

**Results:** With the hierarchical cluster analysis the cases could be grouped into two main clusters. Patients included in cluster 1 [45 cases] had higher rates of osteoarthropathy, cancer, urinary tract infection and hyponatraemia, while cluster 2 [36 cases] was characterized by valvulopathy, atrial fibrillation, heart failure, acute pulmonary insufficiency and pneumonia.

**Discussion and Conclusion:** Based on clinical characteristics, we identified two subgroups of delirious patients with different pattern of risk factors. Cluster 1 reflects deregulation states of different physiological mechanisms during *delirium* since patients in this cluster seem to have disorders affecting multiple organs/systems. Common pathophysiological pathways are likely to include systemic inflammation, pain and electrolyte imbalance. Cluster 2 was constituted by cardiopulmonary symptoms that are associated with both chronic and acute reduction of blood flow and/or oxygenation to the brain which can lead to cerebral hypoperfusion and a

neurovascular unit energy crisis. Known predisposing factors of *delirium*, such as age and pre-existing dementia, were similar between groups.

**Keywords:** *delirium*, aging, acute medical condition, dementia, risk factors

## Background

*Delirium* is a neuropsychiatric syndrome clinically characterised by disturbed consciousness, attention, cognition and perception that is caused by the direct physiological consequences of a general medical condition, substance intoxication/withdrawal, exposure to a toxin or to multiple etiologies. It develops over a short period of time and tends to fluctuate in severity during the course of the day (American Psychiatric Association, 2013). This syndrome is a result of simultaneous interactions between pre-existing predisposing factors (e.g. advanced age, dementia) and acute precipitants (e.g. surgical trauma, infection, medications) (Cerejeira et al., 2011b).

Rates of *delirium* have been extensively studied in various care settings to determine *delirium* prevalence and incidence. In acute medical wards prevalence of *delirium* at admission ranges from 10 to 31%, and incidence of new *delirium* per admission ranges from 3 to 29% (Ahmed et al., 2014). *Delirium* is also a common complication in elderly subjects undergoing surgical procedures with the highest rates after acute surgery for hip fracture, major cardiac surgery and vascular surgery (Ellard et al., 2014; Castro et al., 2014). In intensive care units *delirium* affects 35 to 80% of ventilated patients (Ely et al., 2004) and 40 to 60% of nonventilated patients (Skrobik, 2009; Thomason et al., 2005). The emergence of a *delirium* episode during hospitalization is independently associated with higher morbidity and mortality rates, prolonged hospital stay as well as worse functional recovery and increased cognitive deterioration following hospital discharge (Smith et al., 2015). These adverse outcomes have been reported in different clinical settings (e.g. medical, surgical, intensive care) and after controlling for relevant variables (e.g. comorbidity burden, severity of acute illness, medications). Poor outcomes in delirious medical inpatients are associated with older age,

activities of daily living (ADL) dependence, the presence of acute respiratory failure, hypoxia, and *delirium* severity (Dasgupta et al., 2014).

Despite being a condition strongly associated with adverse outcomes, healthcare professionals only recognise 20-50% of the cases of *delirium* (Marcantonio, 2012). The misdiagnosis is partly caused by the fluctuating nature of *delirium*, overlap with dementia, lack of a formal cognitive assessment, the under-appreciation of its clinical consequences, and a failure to consider the diagnosis as important (Fortini et al., 2013). Early recognition and prompt intervention to identify, and then modify, risk factors associated with *delirium* have been shown to be effective in reducing the incidence and improving outcomes of *delirium* (Cerejeira et al., 2011b). Thus, the National Institute for Health and Care Excellence (NICE) suggests screening for possible *delirium* based on four risk factors (age 65 or over, dementia, presentation with hip fracture and severity of illness) and implementing a tailored intervention to each patient (National Institute for Health and Clinical Excellence, 2010).

Case-control studies have been used to identify risk factors of *delirium* by determining which variables are different between subjects with and without *delirium* (Bucerius et al, 2004; Isfandiaty et al, 2012; Fortini et al, 2013; Seo et al, 2014). Therefore, prior research has identified a diversity of *delirium* predisposing and precipitant factors across different clinical populations. Predisposing factors are individual features rendering the subjects more vulnerable to cope with acute noxious insults or precipitating factors. For example, subjects with advanced age, pre-existing cognitive impairment and poor general health status can develop *delirium* when exposed to even minor acute disturbances (e.g. urinary tract infection, electrolyte imbalance, anticholinergic drug). Conversely, *delirium* can occur in young healthy subjects when the precipitant factors are strong enough to disrupt brain function (e.g. sepsis).

Precipitant factors for *delirium* differ according to the acute underlying medical or surgical condition and between different clinical settings (e.g. type of anaesthetic agents or surgical procedures). The most common precipitant factors for *delirium* include acute diseases, metabolic conditions, medications, iatrogenic complications, surgery, trauma and uncontrolled pain. Patients with higher number of comorbidities and with dementia need somewhat less triggering factors when falling into *delirium* (Hölttä et al., 2014). Adequate knowledge of *delirium* risk factors is crucial to implement preventive measures as several factors are modifiable. However, the particular etiologic role of each risk factor has not been determined. Indeed, from all currently available studies, it is apparent that most cases of *delirium* involve the simultaneous interaction of several factors, each one increasing the risk only marginally, in line with the so-called multifactorial model of *delirium* (Cerejeira et al., 2010). Therefore, identifying subgroups of delirious patients showing a similar pattern of risk factors is a clinically important research objective. This has a potential to be used to predict patients more susceptible to develop *delirium* and allow the definition of more targeted interventions according to the presence of co-occurring risk factors.

Given the small individual effect sizes of the several identified risk factors, *delirium* pathophysiology is likely to involve the interaction of multiple systems eliciting neurochemical abnormalities and brain dysfunction (Cerejeira et al., 2010). Cholinergic neurotransmission has long been recognized to be involved in *delirium* pathophysiology (Cerejeira et al., 2011a). More recently, cholinergic deficit has been proposed as a "final pathway" to *delirium* regardless of the initial insult (Trzepacz, 2000). Other proposed hypothesis for *delirium* pathophysiology include decreased oxidative metabolism, dysfunction of other neurotransmitters (dopamine, norepinephrine, glutamate, serotonin, GABA), abnormal signal transduction, changes in blood-brain barrier permeability, endocrine

abnormalities and increased inflammatory response (Maldonado, 2008). Irrespective of the underlying causes, a common feature of *delirium* pathophysiology is the acute and transient impairment in the homeostatic balance of the Central Nervous System (CNS) comparable to the concepts of renal or hepatic insufficiency (Cerejeira et al., 2013). In health, the conjoined action of several body systems is crucial to recover stability and regain homeostasis (Cerejeira et al., 2013). Understanding the physiological characteristics of subjects prone to develop acute confusion when exposed to acute stress factors, therefore, is of outmost importance (Cerejeira et al., 2013). Elucidating how distinct etiological factors of *delirium* occur simultaneously in subgroups of patients will have significant impact in disclosing the poorly defined pathophysiology of this syndrome. Indeed, it is likely that risk factors occurring more frequently together share common pathways. However, the co-occurrence of risk factors has rarely been addressed in the field of *delirium*.

The aim of this study is to identify sub-groups of risk factors in a sample of elderly patients who developed *delirium* during their hospitalization for an acute medical condition. Hereafter, these data will permit to implement preventing strategies that are essential to significantly reduce the occurrence of this serious condition.

## Materials and methods

### 1. Sample

An observational and cross-sectional study was performed in the Department of Internal Medicine of a university hospital (Centro Hospitalar Universitário de Coimbra, Portugal). All patients aged 65 years old or over, hospitalized with an acute medical condition, between January 2011 and September 2014, and diagnosed with *delirium* by the Liaison Old Age Psychiatric (LOAP) team were eligible to enter the study. The final sample consisted of 82 patients.

### 2. Procedures

All patients referred by the treating medical team to LOAP during hospitalization were assessed with the Confusion Assessment Method (CAM) for the presence of *delirium*. The CAM is a bedside instrument designed to operationalize the symptoms of *delirium* according to Diagnostic and Statistical Manual of Mental Disorders (DSM)-III-R. The diagnostic algorithm assesses four features: 1) acute onset and fluctuating course; 2) inattention; 3) disorganized thinking; 4) altered level of consciousness. *Delirium* is diagnosed when both 1) and 2) are present and at least one of other two (Inouye et al., 1990). Positive cases of *delirium* (according to CAM criteria) were confirmed with DSM-IV-TR criteria (American Psychiatric Association, 2000). In addition to the clinical interview, the nurse in charge of the patient's care was interviewed probing for recent changes to and fluctuations in mental state, altered consciousness, confusion and disorganised conversation and whether they thought that the patient had *delirium*. Medical documentation of possible *delirium* was ascertained by reviewing medical notes for reports of *delirium* or proxy terms such as "confusion". Patients

were excluded from the current study if their clinical condition did not allow the clinical assessment of mental status.

The presence of dementia was evaluated using the *Informant Questionnaire on Cognitive Decline in the Elderly* (IQCODE-SF) (Jorm, 1994). The principal caregiver (formal or informal) was interviewed for the possible presence of global cognitive decline before admission. The principal caregiver was asked to recollect the situation 2 weeks before the current admission and compare it with the situation 10 years earlier. Patients with a mean score of 3.9 or higher were considered to have global cognitive impairment and a diagnosis of dementia was generated after a structured clinical assessment based on operationalised DSM–IV criteria. Sociodemografic characteristics, acute medical conditions and chronic medical comorbidities were obtained from the clinical file.

The procedures and rationale for the study were explained to all patients and relatives but because many patients had cognitive impairment at study entry it was presumed that many were not capable of giving informed written consent. Because of the noninvasive nature of the study, patient assent was complemented with proxy consent from next of kin (where possible) or a responsible caregiver for all participants, in accordance with the Helsinki Guidelines for medical research involving human participants.

**3. Statistic analysis**

The data were entered on an anonymized database. The statistical analysis was performed using PASW Statistics 22.0 software (Chicago, Illinois, USA). A hierarchical cluster analysis was carried out using Ward's method applying squared Euclidean Distance as the distance or

similarity measure. The aim of this statistical method was to find relatively homogeneous clusters of cases based on measured characteristics.

$\chi 2$ and t-Student tests were performed to identified variables with statistically significant differences (p value $<0.05$) between the clusters. The risk factors with a statistically significant difference between the two clusters were incorporated in the cluster in which that factor was more prevalent.

## Results

The final sample included 82 subjects with a mean age of 79.7 ± 6.4 years old ranging from 65 to 97 years old. Most were male, married, with low educational level, living either with spouses or with family and receiving informal care at home (**Table 1**).

**Table 1.** Demographic characteristic of the sample (n=82)

| | | | |
|---|---|---|---|
| **Age**[a] | 79.70±6.448 | **Living conditions** | |
| **Gender (male)** | 47 (57.3%) | Living alone | 13 (15.9%) |
| **Marital status** | | Living with spouses | 22 (26.8%) |
| Married | 41 (50%) | Living with family | 21 (25.6%) |
| Widower | 33 (40.2%) | Living in an institution | 25 (30.5%) |
| Other | 8 (9.8%) | Other | 1 (1.2%) |
| **Educational level** | | **Primary caregiver** | |
| Illiterate | 11 (13.4%) | Informal | 55 (67.1%) |
| Can read and write | 55 (67.1%) | Formal | 27 (32.9%) |
| 1-4 years | 12 (14.6%) | | |
| > 4 years | 4 (4.8%) | | |

[a] Mean±standard deviation.

The results are presented in number and proportion of the total sample (%).

In a significant proportion of the sample (21.9%) it was not possible to assess cognition with Mini Mental State Examination (MMSE). Globally, more frequent disorders in patients with *delirium* were hypertension (65.4%), pre-existing dementia (42%), atrial fibrillation (32.1%), diabetes mellitus (30.9%), heart failure (28.4%) and acute respiratory insufficiency (22.2%).

Patients with cancer were grouped into one variable which included 1 case of pituitary tumour, 2 of stomach cancer, 1 of prostatic adenocarcinoma, 1 of lung cancer, 4 of breast cancer (1 with lung and bones metastases and 1 with hepatic metastases), 1 colorectal cancer and 1 Hodgkin's lymphoma. The variable osteartropathy represents 1 case of chronic

osteomyelitis, 11 of osteoarthritis, 3 of osteoporosis, 1 of ankylosing spondylitis and 1 of spondyloarthropathy.

With the hierarchical cluster analysis (HCA) the cases could be successfully grouped into two main clusters or domains (**Table 2**). Cluster 1 contains 45 cases and cluster 2 contains 36 cases (**Figure 1**). HCA was performed on the analytical data of all the 81 cases because one outlier's case was excluded of the total sample.

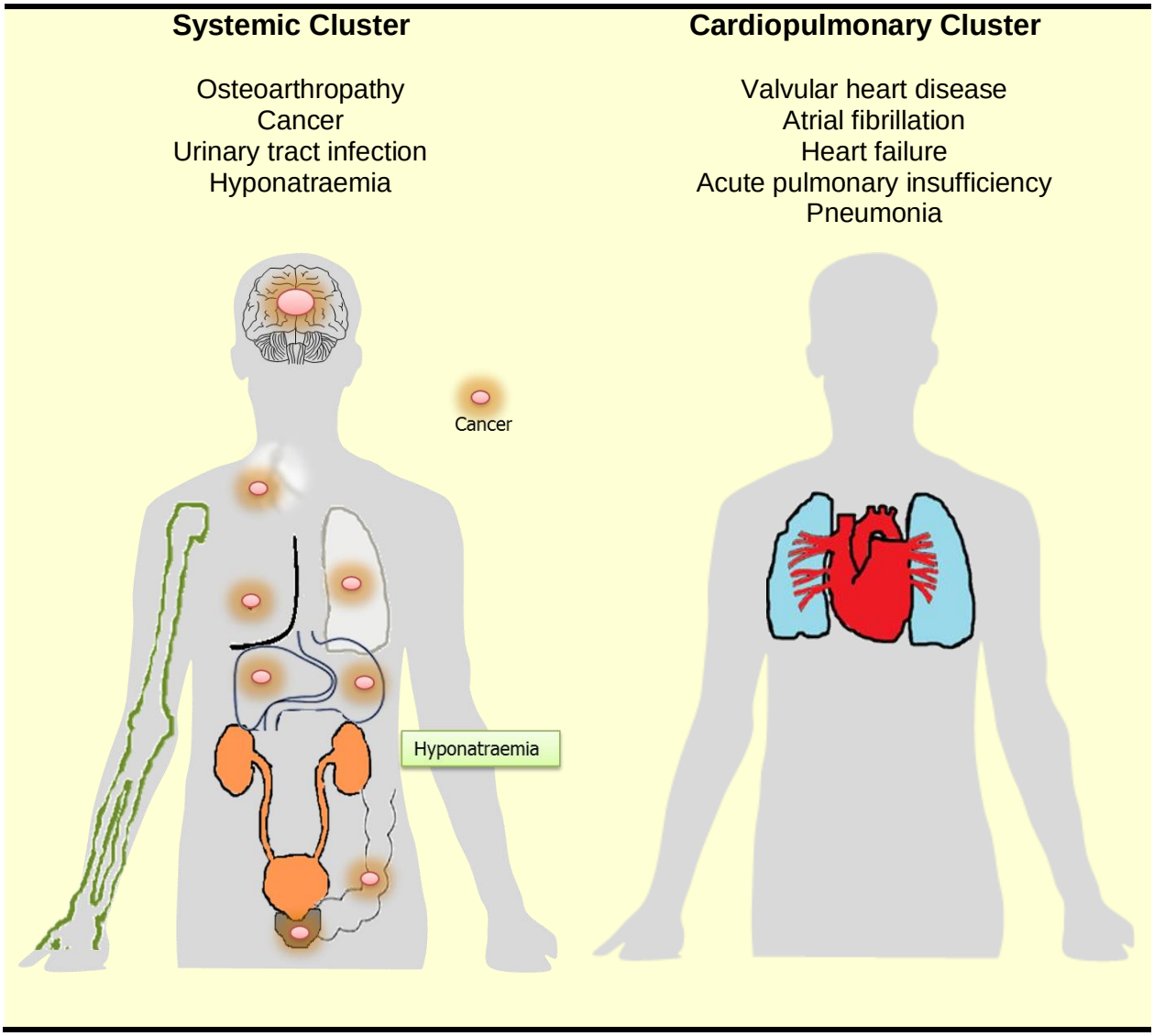
**Table 2.** Frequency of medical conditions in total sample (n=81), cluster 1 and cluster 2

| System | Total sample | Cluster 1 | Cluster 2 | P value |
|---|---|---|---|---|
| **Cardiovascular** | | | | |
| Pacemaker | 4 (4,9%) | 2 (4,4%) | 2 (5,6%) | 0,819[a] |
| Valvular Heart Disease | 3 (3,7%) | 0 (0%) | 3 (8,3%) | **0,048**[a] |
| Acute myocardial infarction | 5 (6,2%) | 1 (2,2%) | 4 (11,1%) | 0,099[a] |
| Hypertension | 53 (65,4%) | 30 (66,7%) | 23 (63,9%) | 0,794[a] |
| Atrial fibrillation | 26 (32,1%) | 3 (6,7%) | 23 (63,9%) | **0,000**[a] |
| Heart failure | 23 (28,4%) | 2 (4,4%) | 21 (58,3%) | **0,000**[a] |
| Endocarditis | 2 (2,5%) | 1 (2,2%) | 1 (2,8%) | 0,873[a] |
| Decompensated heart failure | 9 (11,1%) | 3 (6,7%) | 6 (16,7%) | 0,155[a] |
| **Respiratory** | | | | |
| COPD | 9 (11,1%) | 3 (6,7%) | 6 (16,7%) | 0,155[a] |
| Pulmonary thromboembolism | 2 (2,5%) | 1 (2,2%) | 1 (2,8%) | 0,873[a] |
| Acute respiratory insufficiency | 18 (22,2%) | 3 (6,7%) | 15 (41,7%) | **0,000**[a] |
| Tracheobronchitis | 6 (7,4%) | 2 (4,4%) | 4 (11,1%) | 0,255[a] |
| Pneumonia | 34 (42%) | 13 (28,9%) | 21 (58,3%) | **0,008**[a] |
| Pleural effusion | 2 (2,5%) | 0 (0%) | 2 (5,6%) | 0,109[a] |
| **Hydroelectrolytic disturbances** | | | | |
| Dehydration | 1 (1,2%) | 1 (2,2%) | 0 (0%) | 0,368[a] |
| Hypocalcaemia | 1 (1,2%) | 1 (2,2%) | 0 (0%) | 0,368[a] |
| Acute anemia | 3 (3,7%) | 3 (6,7%) | 0 (0%) | 0,114[a] |
| Hyperkalaemia | 2 (2,5%) | 2 (4,4%) | 0 (0%) | 0,2[a] |
| Hypokalaemia | 1 (1,2%) | 1 (2,2%) | 0 (0%) | 0,368[a] |
| Hypernatraemia | 2 (2,5%) | 2 (4,4%) | 0 (0%) | 0,2[a] |
| Hyponatraemia | 11 (13,6%) | 11 (24,4%) | 0 (0%) | **0,001**[a] |
| **Urinary system** | | | | |
| Hyperuricemia | 7 (8,6%) | 3 (6,7%) | 4 (11,1%) | 0,479[a] |
| Chronic renal insufficiency | 8 (9,9%) | 3 (6,7%) | 5 (13,9%) | 0,279[a] |
| Acute renal insufficiency | 13 (16%) | 8 (17,8%) | 5 (13,9%) | 0,636[a] |
| Acute exacerbation of chronic renal failure | 7 (8,6%) | 4 (8,9%) | 3 (8,3%) | 0,93[a] |

| | | | | |
|---|---|---|---|---|
| Urinary tract infection | 16 (19,8%) | 14 (31,1%) | 2 (5,6%) | **0,004**[a] |
| Benign prostate hyperplasia | 9 (11,1%) | 4 (8,9%) | 5 (13,9%) | 0,477[a] |
| **Endocrine System** | | | | |
| Hypothyroidism | 6 (7,4%) | 5 (11,1%) | 1 (2,8%) | 0,155[a] |
| Obesity | 4 (4,9%) | 1 (2,2%) | 3 (8,3%) | 0,207[a] |
| Diabetes mellitus | 25 (30,9%) | 14 (31,1%) | 11 (30,6%) | 0,957[a] |
| Dyslipidaemia | 20 (24,7%) | 9 (20%) | 11 (30,6%) | 0,274[a] |
| **Gastrointestinal system** | | | | |
| Alcoholism | 3 (3,7%) | 3 (6,7%) | 0 (0%) | 0,114[a] |
| Cholestasis | 2 (2,5%) | 1 (2,2%) | 1 (2,8%) | 0,873[a] |
| Diarrhea | 1 (1,2%) | 1 (2,2%) | 0 (0%) | 0,368[a] |
| Constipation | 2 (2,5%) | 0 (0%) | 2 (5,6%) | 0,109[a] |
| **Neurologic system** | | | | |
| Epilepsy | 2 (2,5%) | 2 (4,4%) | 0 (0%) | 0,2[a] |
| Pre-existing dementia | 34 (42%) | 17 (37,8%) | 17 (47,2%) | 0,392[a] |
| Stroke | 11 (13,6%) | 5 (11,1%) | 6 (16,7%) | 0,468[a] |
| Traumatic brain injury | 2 (2,5%) | 0 (0%) | 2 (5,6%) | 0,109[a] |
| **Other** | | | | |
| Osteoarthropathy | 16 (19,8%) | 15 (33,3%) | 1 (2,8%) | **0,001**[a] |
| Cancert | 11 (13,6%) | 11 (24,4%) | 0 (0%) | **0,001**[a] |
| Rhabdomyolysis | 4 (4,9%) | 2 (4,4%) | 2 (5,6%) | 0,819[a] |
| Sepsis | 4 (4,9%) | 3 (6,7%) | 1 (2,8%) | 0,422[a] |

The values are expressed as number and percentages.
[a] $\chi 2$ test.
[b] Mean±standard deviation.
[c] t-Student test.

**Figure 1.** Systemic and Cardiopulmonary Clusters in subjects with *delirium*



## Discussion and conclusions

Although a single factor can lead to *delirium*, usually this syndrome is multifactorial in elderly people. Since *delirium* has a complex and heterogeneous etiology we ought to determine in what extent different sets of interacting factors are present in elderly subjects with *delirium*. Identifying subgroups of patients sharing identical risk factors can lead the search for common underlying pathophysiologic patterns and to the development of more focused treatment strategies.

To the best of our knowledge, this is the first study to use cluster analysis to categorize delirious elderly patients according to their medical comorbidities and other associated risk factors of *delirium*. Based on clinical characteristics, we identified two subgroups of delirious patients with different pattern of risk factors. The first cluster had higher rates of osteoarthropathy, cancer, urinary tract infection and hyponatremia. Subjects included in the second cluster were characterized by the presence of cardiopulmonary dysfunction, such as valvular heart disease, atrial fibrillation, heart failure, pneumonia and acute respiratory insufficiency. Known predisposing factors of *delirium*, such as age and pre-existing dementia, were similar between groups. In line with prior studies, dementia prevalence in the total sample was 42%.

*Cluster 1*

Cluster 1 seems to reflect deregulation of different physiological mechanisms during *delirium* since patients in this cluster have disorders affecting multiple organs/systems. Common pathophysiological pathways in this subgroup are likely to include systemic inflammation, pain and electrolyte imbalance. Each condition present in cluster 1 has been previously

associated with *delirium*, albeit not consistently. Osteoarthrosis is a debilitating degenerative joint disease particularly affecting weight bearing joints, principally the hips and knees. Classically, osteoarthrosis has been considered solely as a "wear and tear" disease. However, accumulating evidence demonstrate that soluble inflammatory factors including cytokines, chemokines, adipokines, neuropeptides, and lipid inflammatory mediators have a crucial role in the pathogenesis of this disorder (Wojdasiewicz et al., 2014). In addition, pain is a prominent and disabling symptom of osteoarthrosis. Nociceptive input from the joint is processed via different spinal cord pathways, and inflammation may potentially reduce the threshold for nociceptive stimulus. A peripheral drive to pain is thought to be predominant in 60 to 80% of patients whereas central mechanisms such as dysfunction of descending inhibitory control or altered cortical processing of noxious information, may play a greater role (Lee et al., 2013). *Delirium* is a frequent neurocognitive complication in patients with cancer, particularly in advances phases. Common factors associated with both cancer and *delirium* include metabolic abnormalities, electrolyte disturbances, dehydration, malnutrition, infection, psychotropic drugs, hypoxia, metabolic factors (such as kidney or liver failure and hypoglycemia), hypocalcaemia, anemia, coagulation changes, increased levels of inflammatory markers and chronic pain (Lawlor et al., 2015). The association between sodium abnormalities and *delirium* has been previously identified in a few studies. A high sodium concentration in the postoperative period following cardiac surgery was a predictor for *delirium* (Giltay et al., 2006; Smulter et al., 2013). In non-cardiac surgical patients sodium abnormalities were a risk factor for *delirium*, but because of too few cases of isolated electrolyte disturbances, data on specific electrolyte abnormalities were not reported (Marcantonio et al., 1994). In medical patients, high or low sodium were most commonly associated with increased *delirium* risk (Ahmed, 2014). Hyponatremia is the most common disorder of electrolytes encountered in clinical practice, occurring in 15-30% of acutely or

chronically hospitalized patients (Verbalis et al., 2013). This common disorder remains incompletely understood in many basic areas because of its association with a plethora of underlying disease states, its causation by multiple etiologies with differing pathophysiological mechanisms (Verbalis et al., 2013). Most hyponatremic states are characterized by inappropriate plasma levels of arginine vasopressin (AVP) which, once secreted, binds to the AVP V2 receptor subtype in the kidney collecting ducts and activates the signal transduction cascade resulting in antidiuresis. The association of hyponatremia with increased morbidity and mortality of hospitalized patients across a wide variety of disorders has long been recognized. A direct relation between hyponatremia and brain dysfunction exists as reduced plasma sodium induces brain swelling and increased intracerebral pressure. On the other hand, a rapid correction of hyponatremia can lead to osmotic demyelination. *Delirium* can be a presenting clinical feature of underlying urinary tract infection. Urinary tract infection is associated with the initiation of systemic inflammatory cascades stimulating the production and circulation of compounds including heat shock proteins, tumour necrosis factor-alpha and interleukins. The influence of peripherally circulating inflammatory mediators may affect the brain by altering the activity of the hypothalamic-pituitary axis thereby altering the hormonal environment of the body and nervous system (Balogun et al., 2013).

*Cluster 2*

The second cluster was constituted by factors related to cardiopulmonary function, such as valvular heart disease, atrial fibrillation, heart failure, pneumonia and acute respiratory insufficiency. Since it is unable to store energy, the brain function depends on continuous delivery of oxygen and glucose through blood flow. The brain is a high-flow, low-impedance organ with a high metabolic rate, and typically receives 15% of total cardiac output and 25 to

50% of total body glucose utilization despite accounting for only 2% of total bodyweight. Blood flow to the brain is autoregulated and remains relatively constant over a wide range of mean perfusion pressures. Proper neural function necessitates that the interface between the CNS and the peripheral circulatory system functions as a dynamic regulator of ion balance, a facilitator of nutrient transport, and a barrier to potentially harmful molecules. This homeostatic aspect of the cerebral microcirculation, historically referred to as the "blood-brain barrier", performs these functions through a tightly coordinated interaction between the cerebral microvascular endothelium, astrocytes, pericytes, neurons, and the extracellular matrix, known as the "neurovascular unit" (Hawkins et al., 2005). Thus, under physiological conditions there is a systematic coupling between activation of specific brain function and microcirculation flow activation. Conditions in cluster 2 are associated with both chronic and acute reduction of blood flow and/or oxygenation to the brain which can lead to cerebral hypoperfusion and a neurovascular unit energy crisis. For example, cardiac output is chronically impaired during atrial fibrillation, heart failure and valvular heart disease. Also, patients with these cardiac conditions are at increased risk of asymptomatic or silent cerebral infarction as a result of embolization, a mechanism similar to that of an ischaemic stroke (Udompanich et al., 2013). These neuropathological changes reduce the brain resilience to cope with additional insults (e.g. acute reduction in brain perfusion or oxygenation) and the subject will be more likely to manifest clinical symptoms of acute brain dysfunction (i.e. *delirium*). On the other hand, pneumonia is associated not only with systemic inflammation but also with hypoxia. In conclusion, although the role of vascular disease in the development of *delirium* remains poorly understood our results underlie the role of the cardiopulmonary system dysfunction in the pathophysiology of *delirium*. It is likely that decreased brain perfusion below the lower threshold of autoregulation might lead to an insufficient delivery of glucose and oxygen resulting in acute organ dysfunction and *delirium*. These changes can be

further aggravated following exposure to systemic inflammatory mediators released into circulation and reaching the neurovascular unit, which has been suggested to contribute to *delirium* (Cerejeira et al., 2010). Importantly, this suggests that a thorough evaluation of patients with *delirium* might systematically include the assessment of the cardiovascular and respiratory function linking blood perfusion to brain function.

*Homeostasis and brain-body interaction during acute disease*

The pathophysiological link between *delirium* and a broad array of precipitant factors is difficult to establish as most of these conditions occur without identifiable involvement of the brain. Moreover, how completely different etiological causes may evoke similar symptoms has not yet been satisfactorily explained. So far, it is well established that during threatening conditions, such as infection or injury, it is indispensable that immunological responses are integrated in the full range of homeostatic mechanisms of the body. Consequently, the CNS and the peripheral immune system maintain a dynamic cross-talk to tightly coordinate the innate immune response (Cerejeira et al., 2014). Patients who develop *delirium* may belong to different states of regulatory physiological mechanisms. Primary stress represents the amount of physiological burden exerted on the human body after any acute illness (Giannoudis et al., 2006). It is likely that various pre-existing conditions and co-morbidities present at the patient's admission – for instance, congestive heart failure, electrolyte imbalance, liver failure and infection – can adversely influence the stress response by compromising the patient's homeostatic compensatory mechanisms.

*Methodologic issues*

It was found that only 21.95% of the total sample was able to perform the MMSE. This result is consistent with others found in the literature and suggests that MMSE, which is dependent

on patient collaboration, may not be an adequate instrument to use in older people with an acute medical illness. It can be concluded that there is a necessity of creating new instruments for measuring cognition in these patients.

*Limitations*

It is important to note some limitations of this study. First, not all risk factors noted by other studies were measured (e.g., environmental factors, isolation, use of bladder catheter, physical restraints, pain, nutrition, medication, and sensorial deprivation) what can influence the present results. Second, it can be highlighted the small sample size. Using a larger sample size it is likely that a greater number of clusters could be found. Finally, the study was implemented in a single hospital, and although this is likely to be representative of modern in-patient medical centers, further work replicating these findings elsewhere can further enhance our understanding of how risk factors aggregate in elderly patients with *delirium*.

*Implications and future directions*

This study provides new information about how multiple factors interact and work together in elderly patients to disrupt large-scale neuronal networks in the brain and manifesting as *delirium*. These results may help the identification of individuals at high risk of developing *delirium* who should undergo screening and correction of several different sets of interacting biological factors. These will enable physicians to implement strategies to avoid occurrence of *delirium*, decrease *delirium* duration and improve outcomes. Following this innovative method of analysing risk factors of *delirium*, this study can be a first step to permit new clusters to be identified. Future studies must add more variables such as acute and chronic medication and laboratory tests as well as a larger number of patients.

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