

## Delirium in internal medicine ward – impact on clinical practice

### *Delirium numa enfermaria de Medicina Interna - impacto na prática clínica*

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**ABSTRACT:** *Introduction:* Delirium is common in hospitalized elderly patients. It is defined as an acute and fluctuating, usually reversible, alteration of the level of cognition, attention and consciousness, with a multifactorial etiology, associated with increased morbimortality and costs, however, remains underdiagnosed. We evaluated the occurrence of delirium in an Internal Medicine ward, it's main risk factors and consequences during hospitalization and 3 months after discharge. *Materials and Methods:* prospective 3-month observational study in a ward of a tertiary hospital, using the adaptation of Richmond sedation and agitation scale and the Confusion Assessment Method for the diagnosis of delirium, confirmed by the criteria of the Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> edition. The main risk factors were selected according to the guidelines. Hospitalization consequences and survival at 3 months were evaluated. *Results/Discussion:* In a sample of 297 patients, 26% presented delirious, mostly at admission (73%), with a hyperactive phenotype (50%). These patients were older, with more comorbidities, namely dementia, and less autonomy. Physical restraint, autonomy impairment, and serum potassium levels were identified as independent factors for delirium. It was also associated with higher in-hospital and 3 months mortality, and major burden on health professionals. The application of the scales allowed a greater recognition of this syndrome (12% to 26%), namely the hypoactive forms. *Conclusion:* Delirium was frequent and with a high impact on patients and health professionals.

**RESUMO:** *Introdução:* O delirium é frequente nos doentes idosos internados. Define-se como uma alteração aguda e flutuante ao nível da cognição, atenção e consciência, geralmente reversível e de etiologia multifactorial, com aumento da morbimortalidade e dos custos, mas que permanece sub-diagnosticada. Neste sentido, avaliou-se a ocorrência de delirium numa enfermaria de Medicina Interna, os principais factores de risco e o impacto no episódio de internamento e após 3 meses. *Materiais e Métodos:* estudo prospectivo observacional de 3 meses num serviço de um hospital terciário, com aplicação da escala de sedação e agitação de Richmond adaptada e do Método de Avaliação da Confusão para o rastreio e diagnóstico de delirium, confirmadas pelos critérios do *Diagnostic and Statistical Manual of Mental Disorders, 5ª edição*. Avaliaram-se os principais factores de risco, segundo as *guidelines*, e o impacto no internamento e sobrevida aos 3 meses. *Resultados/Discussão:* Numa amostra de 297 doentes, a ocorrência de delirium foi de 26%, na sua maioria à admissão (73%) e na forma hiperactiva (50%). Estes doentes eram mais idosos, com mais comorbilidades, nomeadamente demência, e menos autonomia. Identificou-se a contenção física, a limitação da autonomia e as alterações do potássio como factores independentes para a ocorrência de delirium. Este associou-se a maior mortalidade no internamento e aos 3 meses, com maior sobrecarga dos profissionais de saúde. A aplicação das escalas permitiu um maior reconhecimento desta patologia (12% para 26%), nomeadamente as formas hipoactivas. *Conclusão:* O delirium foi frequente e com elevado impacto nos doentes e profissionais de saúde.

**Key-words:** delirium, Internal Medicine, elderly, mortality

**Palavras-chave:** delirium, Medicina Interna, idoso, mortalidade

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## INTRODUCTION

With the increase in the average life expectancy and global aging of the population, which in Portugal reaches one of the highest rates in Europe<sup>1,2</sup>, an inherent increase in the elderly and chronic irreversible diseases has been observed. This urges the need for specific and targeted care, often as inpatients, which implies important costs for the health system<sup>3</sup>.

Among the most frequent problems in hospitalizations, *delirium* stands out, particularly in the elderly and end-of-life population<sup>4</sup>. It is a neuropsychiatric syndrome that is characterized by an acute and fluctuating change in cognition, attention and awareness, usually reversible<sup>5</sup>. Despite the poorly clarified pathophysiology, *delirium* appears to result from an acute brain disorder, associated with changes in neurotransmitters (e.g. acetylcholine deficit or dopaminergic deficit)<sup>6</sup>, usually of multifactorial etiology<sup>4</sup>. Among *delirium* main risk factors are old age and dementia, both increasing<sup>6,7</sup>, as well as infection, pain, the use of psychiatric drugs, metabolic and hydro-electrolytic changes<sup>4</sup>.

It is the most common neuropsychiatric syndrome in the hospital setting and one of the six main preventable diseases in the hospitalized elderly, associated with a worse prognosis and a greater number of complications during and after hospitalization<sup>4</sup>. Effectively, *delirium* has a high impact on health care and at a socioeconomic level, namely with increased morbidity and mortality, and it is also cause of suffering from patient and family<sup>4</sup>. However, despite the growing interest in *delirium*, it remains a poorly understood and under-diagnosed entity<sup>4</sup>.

In Portugal, there have been some published works concerning *delirium*, however mostly developed in specific types of patients other than in an Internal Medicine ward (IMW)<sup>8-14</sup>.

There by, the authors intended to assess the occurrence of *delirium* in an IMW and to analyse the impact of the systematic use of tools for its recognition, as well as to identify the main risk factors and consequences associated with this entity and its impact on survival at 3 months.

## MATERIAL AND METHODS

A prospective observational study was carried out for 3 months (March to June 2017) at an IMW of a tertiary and university hospital in Lisbon, Portugal. All patients admitted consecutively to IMW over 18 years of age were included. Patients from other wards, who stayed less than 24 hours in hospital, who did not speak Portuguese or who refused to participate were excluded. The study comprised the first week of hospitalization (7 days) of the selected patients.

The Richmond adapted sedation and agitation scale (RASSad)<sup>15-16</sup> was applied as screening of *delirium*, and it consists of a classification of the degree of psychomotor agitation, from -5 to 4, considering values between -1 and 1 as normal. In patients with *delirium*, values above 1 correspond to hyperactive conditions, and those below -1 to hypoactive. In the presence of degrees of agitation that vary between positive and negative values, it would be classified as a mixed episode. The RASSad was applied to all patients admitted to IMW, without any exclusion criteria, 3 times a day by the nursing team (1 time in each shift).

For the *delirium* diagnosis, the clinical researcher (FQ) applied the translated and validated Portuguese version of the Confusion Assessment Method (CAM)<sup>17</sup> at the first and seventh day of hospitalization; and also in case of complications (any evaluation by the Medical *On call* Team or if more than 2 consecutive altered RASSad evaluations). All cases were confirmed by applying the Diagnostic and Statistical Manual of Mental Disorders 5th edition (DSM – 5), considered the gold standard for the diagnosis of *delirium*.

It was considered *delirium* on admission when present at the beginning or in the first 48 hours, and *delirium* during hospitalization (intercurrent) if it appeared after 48 hours of hospitalization, during the first week.

The identification of *delirium* through the scales was compared with data from a retrospective study on its occurrence (based on the reference to this diagnosis in the clinical file) carried out at the same IMW in an identical period in the previous year, which included 338 patients.

Written informed consent was not obtained due to the non-interventional nature of the study, with a minimum deviation from the usual clinical practice, and because there was no risk for patients (Article 6 of the Oviedo Convention), whose will (and their family members) has always been respected. However, whenever able, verbal consent was obtained from the patient or the caregiver / family member.

Demographic data (gender, age and place of residence) were collected; comorbidities (number and Charlson index)<sup>18</sup>; performance status<sup>19</sup>, which quantifies the impact of the disease on activities of daily living, in an increasing order of disability (0 - active without restrictions, up to 5 - death); the degree of prior autonomy using the Barthel scale<sup>20</sup>, which assesses the ability to independently perform 10 basic activities of daily living on a scale from 0 (dependent) to 100 (totally independent); and the main hospitalization diagnosis. It should be noted that the diagnosis of dementia was considered only if it was previously described in the clinical process or personal history.

After reviewing the literature, there were selected the main factors described as precipitating / predisposing to *delirium*<sup>4,21-22</sup>: previous medication was considered

regarding the type and number of drugs (polymedication: use of 5 or more drugs<sup>23</sup>); medication administered during hospitalization if instituted prior to the identification / diagnosis of the *delirium* episode; clinical and laboratory data regarding the presence of infection (symptoms and signs, elevation of inflammatory parameters, positive microbiological cultures or antibiotic prescription), dehydration (symptoms, signs and changes in the urea / creatinine ratio),

electrolytes changes (135 <sodium> 145 mEq; 3.5 <potassium> 5.5 mEq) and blood glucose (<70 or> 200 mg/dL). The nursing records were also assessed looking for the presence of pressure ulcers, pain, constipation, sleep pattern (normal, reduced or increased), falls or physical restraint use. All these factors were considered only if present prior to the identification / diagnosis of *delirium*.

It was also assessed the possible repercussions and consequences of *delirium*, which accounted for the intervention of the Medical *On-call* Team (number of calls), the need for pharmacological restraint or the application of non-pharmacological measures (e.g. reorientation, low beds, etc.); and requests for Liaison Psychiatry evaluation (number of requests), which gives support to these situations at our institution. Finally, the length of stay in the IMW (until discharge, transfer or death), discharge destination (considering institutionalization as discharge to a Nursing Home or Rehabilitation Care Network), survival to discharge and at 3 months ( by consulting the informatic clinical process and the “Registo de Saúde Eletrônico” Electronic Health Record - RSE) and the number of readmissions in those 3 months, according to the RSE consultation. Data collection was carried out prospectively

by the clinical researcher (FQ) directly with the patient and/ or through the informatic clinical processes, medical and nursing records, and RSE.

Univariate descriptive analysis was performed using the median, mean, standard deviation, and Mann-Whitney test in the case of continuous variables; and proportions and Chi-square or Fisher’s test for categorical variables; an age-adjusted sub-analysis was also performed, given the higher prevalence of *delirium* in the elderly (> 65 and > 80 years). Then, multivariate analysis of risk factors was performed to identify variables with an independent association with *delirium*. A logistic regression model was used, using the Forward Stepwise method, and the goodness of fit was validated by the Hosmer and Lemeshow test. The level of statistical significance adopted was  $p < 0.05$  (95% confidence interval). Survival analysis was also performed at 3 months after discharge (endpoint: mortality from any cause), according to the Kaplan-Meier method and compared using the log-rank test. Statistical analysis was performed using SPSS 22.0® software.

## RESULTS

The final study sample had 297 patients. There were 78 (26%) cases of *delirium*, the majority present at admission (N = 57, 73%) (Figures 1 and 2). Of these, 30% persisted during the first week; and 21 (27%) cases of intercurrent *delirium* were observed (Figure 2).

In this sample, patients with *delirium* were older, had more comorbidities, namely dementia, less previous autonomy and there was a higher rate of institutionalization prior to hospitalization (Table 1).

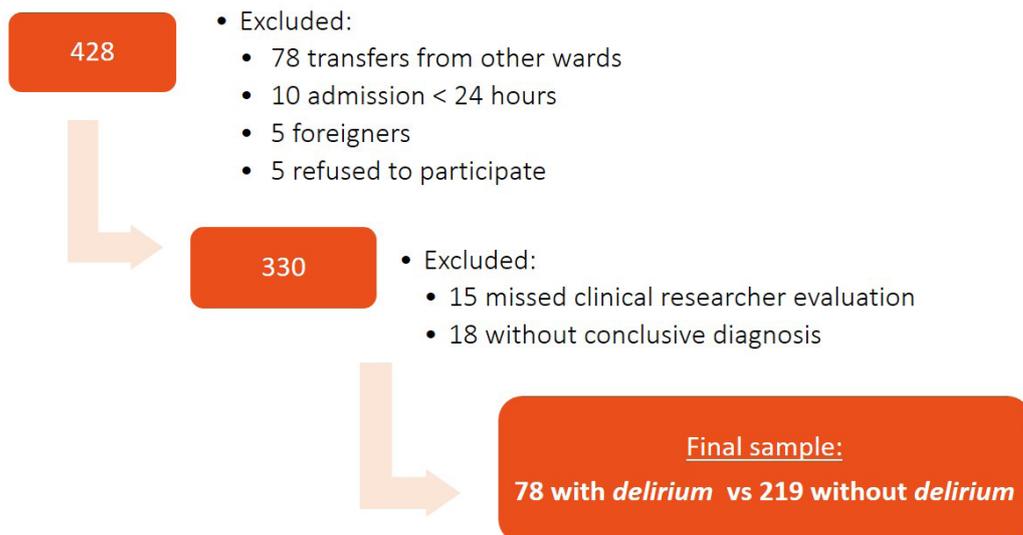


Figure 1 – Study sample selection diagram

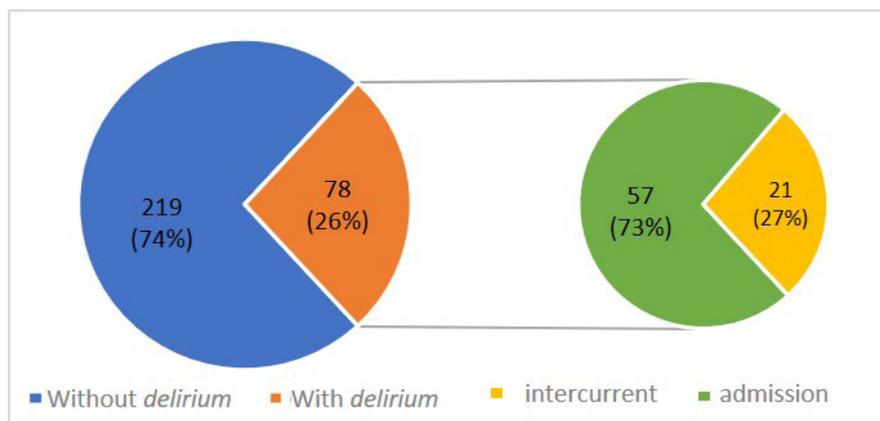


Figure 2 – Delirium occurrence during hospitalization

Table 1 – Sample main risk factors for delirium

Risk factors	No delirium (219) N (%)	With delirium (78) N (%)	Univariate OR (CI 95%) p-value*	Multivariate OR (CI 95%) p-value**
Age (mean ± S.D.)	73±15.11	82±10.43	<0.0001 <sup>a</sup>	
Female	117 (53)	47 (60)	0.76 (0.45-1.28)	
Male	102 (47)	31 (40)	0.297 <sup>b</sup>	
Comorbidities (n°) (mean ± S.D.)	7±3.06	6±2.45	0.023 <sup>a</sup>	
Charlson Index (median)	6	6	0.324 <sup>a</sup>	
Dementia	27 (12)	29 (37)	4.21 (2.29-7.75) <0.0001 <sup>b</sup>	
Residence				
Home	199 (91)	63 (81)	0.42 (0.20-0.87)	
Nursing home	18 (8)	13 (17)	0.018 <sup>b</sup>	
Other	2 (1)	2 (2)		
Barthel Index (median)	90	50	<0.0001 <sup>a</sup>	0.97 (0.96-0.99)
Performance Status (median)	1	2	<0.0001 <sup>a</sup>	<0.0001
Polymedication	140 (64)	48 (62)	0.90(0.53-1.54) 0.707 <sup>b</sup>	
Risk Drugs mean± S.D. (min-max)	2±1.76 (0-9)	3±1.94 (0-8)	0.99 (0.48-2.02) 0.977 <sup>b</sup>	
Opioids	27 (12)	12 (15)	0.77 (0.37-1.61) 0.493 <sup>b</sup>	
Corticosteroids	46 (21)	14 (18)	1.22 (0.63-2.36) 0.564 <sup>b</sup>	
Benzodiazepines	98 (45)	30 (38)	1.30 (0.76-2.20) 0.336 <sup>b</sup>	
Antipsychotics	41 (19)	46 (59)	0.16 (0.09-0.28) <0.0001 <sup>b</sup>	
Antihistaminic	19 (9)	8 (10)	0.83 (0.35-1.98) 0.677 <sup>b</sup>	
Antiemetics	35 (16)	7 (9)	1.93 (0.82-4.54) 0.127 <sup>b</sup>	
Antidepressives	31 (14)	9 (12)	1.26 (0.57-2.79) 0.561 <sup>b</sup>	
Antiparkinsonics	6 (3)	7 (9)	0.29 (0.09-0.88) 0.046 <sup>c</sup>	
Antiepileptics'	23 (11)	10 (13)	0.80 (0.36-1.76) 0.576 <sup>b</sup>	
Other drugs	28 (13)	6 (8)	1.76 (0.70-4.43) 0.225 <sup>b</sup>	

continue

**Table 1** – Sample main risk factors for *delirium*

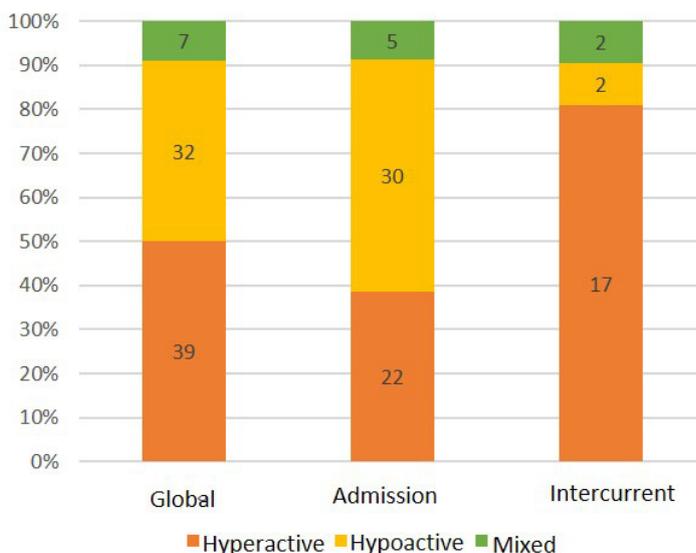
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Risk factors	No delirium (219) N (%)	With delirium (78) N (%)	Univariate OR (CI 95%) p-value*	Multivariate OR (CI 95%) p-value**
Infection	109 (50)	58 (74)	2.93 (1.65-5.19) <b>&lt;0.0001<sup>b</sup></b>	
Dehydration	103 (47)	40 (51)	1.19 (0.71-1.99) 0.519 <sup>b</sup>	
Constipation	59 (27)	33 (42)	1.99 (1.16-3.41) <b>0.012<sup>b</sup></b>	
Pressure ulcer	12 (5)	19 (24)	5.56 (2.55-12.10) <b>&lt;0.0001<sup>b</sup></b>	
Urinary catheter	45 (21)	28 (36)	2.21 (1.25-3.90) <b>0.006<sup>b</sup></b>	
Altered sleep pattern	87 (40)	41 (53)	2.31 (1.27-4.21) <b>0.005<sup>b</sup></b>	
Falls	6 (3)	5 (6)	2.43 (0.72-8.21) 0.140 <sup>c</sup>	
Physical restrain	9 (4)	41 (53)	25.86 (11.6-57.64) <b>&lt;0.0001<sup>c</sup></b>	68.59 (16.37-287.5) <b>&lt;0.0001</b>
Electrolyte levels	71 (32)	43 (55)	2.49 (1.47-4.23) <b>0.001<sup>b</sup></b>	3.64; (1.12-11.85) <b>0.032</b>
- Sodium	48 (22)	27 (35)	1.85 (1.05-3.26) <b>0.031<sup>b</sup></b>	
- Potassium	38 (17)	23 (29)	1.92 (1.05-3.49) <b>0.032<sup>b</sup></b>	
Glycemia	18 (8)	14 (18)	2.93 (1.32-6.48) <b>0.006<sup>b</sup></b>	

\* values with statistical significance are in bold; \*\*Hosmer e Lemeshow Test p= 0.731; a) Mann-Whitney test; b) Qui-square test; c) Fisher test.

The most frequent main diagnoses were from cardiovascular and respiratory groups (29%, N = 97 and 24%, N = 79 respectively), with a high prevalence of infection, regardless of the underlying pathology (43%, N = 143).

As for the psychomotor phenotype, the hyperactive form was the most common (N = 39, 50%), noting, however, that, in cases where present at admission, hypoactive forms of *delirium* prevailed (N = 30, 53%) (Figure 3).



**Figure 3** - Delirium psychomotor phenotype (RASSad)

We highlight the significant association between delirium and previous autonomy ( $p < 0.0001$ , OR = 0.97, 95% CI 0.96-0.99), application of physical restraint measures ( $p < 0.0001$ , OR = 68.59, 95% CI 16.37-287.5), and altered potassium levels ( $p = 0.032$ ; OR = 3.64, 95% CI 1.12-11.85), according to the multivariate analysis (Table 1).

The need for evaluation by Medical *On Call* Team or Liaison Psychiatry was higher in the group with delirium (Table 2) and was associated with greater use of

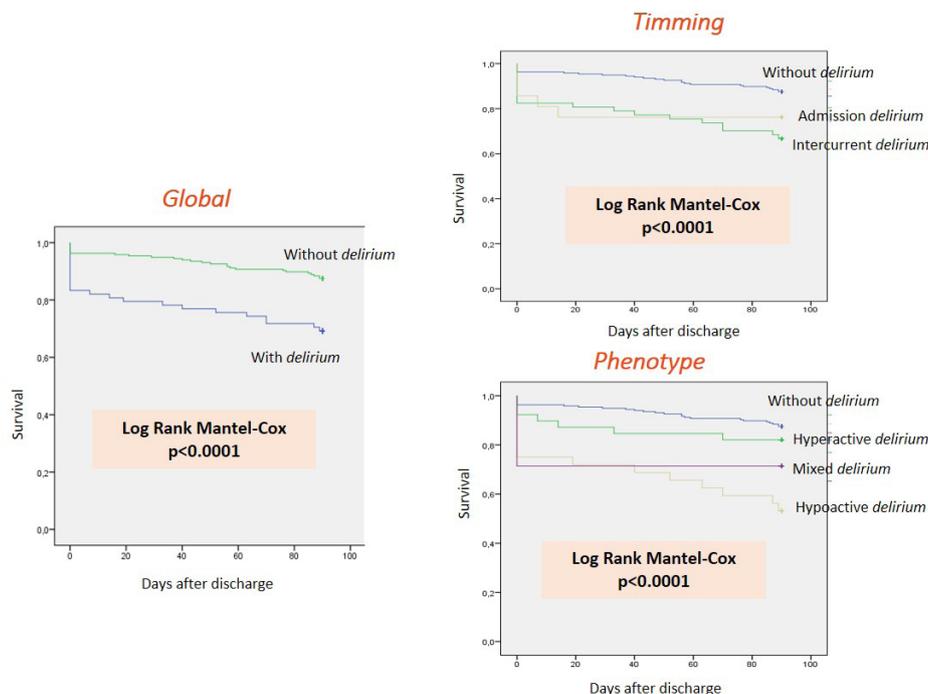
pharmacological therapy, being a possible indicator of a greater burden to health professionals in this pathology. It was also observed that this entity was more frequent among palliative patients ( $N = 17/35$ ;  $p < 0.0001$ ), namely in those at the end of life ( $N = 13/19$ ,  $p > 0.0001$ ).

In the delirium sample there was a trend towards a longer hospital stay, but without statistical significance ( $p = 0.055$ ); with an in-hospital mortality almost 3 times higher, and 2 times higher at 3 months after discharge in this group (Table 2 and Figure 4).

**Table 2** – Consequences during hospitalization and 3 months after discharge in the sample groups with and without delirium

Consequences	No delirium (219) N (%)	With delirium (78) N (%)	OR (CI 95%)	p-value*
<b>Medical <i>On call</i> Team</b>	20 (9)	36 (46)	8.53 (4.50-16.17)	<b>&lt;0.0001<sup>b</sup></b>
<b>Pharmacological restrains</b>	9 (4)	35 (45)	18.99 (8.51-42.38)	<b>&lt;0.0001<sup>b</sup></b>
Liaison Psychiatry	9 (4)	13 (17)	4.67 (1.91-11.41)	<b>&lt;0.0001<sup>b</sup></b>
<b>Length of stay - days (mean ± S.D.)</b>	11±9.62	13±11.66		0.055 <sup>a</sup>
<b>Local of Discharge</b> (without deaths during admission)				
Transferred	19 (9)	6 (8)	0.87 (0.40-1.89)	0.719 <sup>b</sup>
Same	184 (84)	55 (70)		
Altered	10 (4)	4 (5)		
<b>Deaths during admission</b>	6 (3)	13 (17)	7.1 (2.60-19.42)	<b>&lt;0.0001<sup>c</sup></b>
<b>3 months survival</b>	189 (86)	54 (69)	3.1 (1.67-5.83)	<b>&lt;0.0001<sup>b</sup></b>
<b>3 months readmission</b>	72 (33)	30 (38)	0.89 (0.49-1.61)	0.695 <sup>b</sup>

\* values with statistical significance are in bold; a) Mann-Whitney test; b) Qui-square test; c) Fisher test.



**Figure 4** – Sample survival at 3 months after discharge (global, regarding the moment of hospitalization and the psychomotor phenotype)

## DISCUSSION

In a sample of 297 patients, the *delirium* occurrence was 26%, mostly on admission (73%) and in the hyperactive form (50%). These patients were older, had more comorbidities, namely previous dementia, and less autonomy. Physical restraint, limited autonomy and altered potassium levels were identified as independent factors for *delirium* occurrence. It was associated with higher mortality at hospitalization and at 3 months after discharge, as well as with a greater burden on health professionals. The systematic use of scales allowed a greater recognition of this pathology (12% to 26%), namely its hypoactive forms.

In fact, this study corroborated the previous evidence that *delirium* is a frequent pathology that remains underdiagnosed and whose recognition can be improved with the implementation of diagnostic scales<sup>24,25</sup>. In fact, its application has improved *delirium* identification because, compared to the retrospective study in the same IMW, since there was a 26% incidence in the prospective study, compared to 12% in the previous year, without the scales.

This incidence is in accordance with that described in the literature (11-34%)<sup>4,26</sup>, and was similar to a study carried out in Portugal (although performed in an Emergency Department), with an incidence of 20%<sup>10</sup>.

There was an higher incidence of *delirium* at admission (N = 57; 73%), also as it is described in some studies, although the published results are somewhat discrepant.<sup>27</sup> The cases at admission can result from several factors, as in this Hospital many patients remain in the Emergency Department for some time before admission to the IMW, which can enhance the development of *delirium*, namely due to frequent changes in the bed / location of the patient; the lack of established routines and environmental conditions (eg light, noise, time references such as clocks etc.) that are not very favorable<sup>28</sup>.

As for the psychomotor phenotype, the application of the scales also allowed for a better characterization, namely of the hypoactive forms (retrospectively 2%, N = 1/41 vs. prospectively 41%, N = 32/78), described as more frequent, but less recognized and associated with a worse prognosis<sup>4,29-30</sup>. Nevertheless, most frequently identified psychomotor form of *delirium* in this study was the hyperactive (50%).

Among the factors associated with *delirium*, hospitalization, which was present in all cases, is in itself an important environmental change and is well established as a precipitant of this pathology<sup>4,28,31</sup>. Among the other elements analysed, there was a strong association with physical restraint, with a 5.5 times higher risk of *delirium*. Despite being a contraindicated practice, with clear recommendations from the "Direcção Geral de Saúde"<sup>32</sup>, it is still frequent in the wards, claiming to promote greater safety for the patient. And it is well documented as a precipitant and for the persistence of *delirium* in

hospitalized patients<sup>4,22,28,33</sup>. The effects of drugs are other well established precipitant<sup>4,34</sup>, with some classes at greater risk for acting on the pathophysiological pathways involved. In *delirium*, particularly the cholinergic and dopaminergic pathways<sup>34,35</sup>. The use of antipsychotics was a factor independently related to the occurrence of hyperactive *delirium*, even after adjusting for age; however, by the methodology of this study, it is difficult to identify the reason for the prescription and to take conclusions whether it was a precipitant or if it is just a frequently prescribed class. Antipsychotics due to their action at the level of dopaminergic receptors, reducing dopamine, have been suggested for *delirium* treatment, despite some inconsistency in terms of scientific evidence<sup>34,36</sup>.

Altered electrolytes levels, such as sodium and potassium, as well as glycemia values, have been associated with *delirium*, as observed in this study (Table 1). Although more scientific evidence is needed to establish this relationship<sup>4,28</sup>, it is considered that it is consequence of these elements action in some of the main pathophysiological pathways involved in *delirium*<sup>4,35</sup>.

The impact of *delirium*, both in terms of the burden of health professionals and in the survival of patients, was clear in this study as previously documented<sup>4,26-28,35</sup>.

Some authors argue that mortality maybe due to *delirium* itself<sup>21</sup>, however it is not clear whether it is not the consequence of the underlying factors that lead to death and also made patients more predisposed to *delirium*. It was found that, in most cases, deaths occurred early, in the first week of hospitalization, which reflects the severity of the clinical conditions in these patients.

The strengths of this study are the high number of patients included; the systematic application of scales for the identification of *delirium* (greater than 85%); as well as the added value of using cognitive tests in a typology in which patients are at high risk of cognitive changes which often are not identified<sup>37</sup>. Furthermore, the tools used were simple and fast to apply, with high specificity (> 97 %), without a great deviation from the usual clinical practice, so the author believe that they can be integrated into the daily routine without a significant increase in work overload. Among the main limitations identified are the scales of diagnosis of *delirium* application only in 2 moments (except for complications) and only by a single investigator. However, the rate of *delirium*, its risks factors and the association with mortality are in accordance with previous studies, suggesting that the reality of this Portuguese IMW will be similar to that of those studies. This was the first work about *delirium* carried out at this Hospital and, from the research carried out, the first also at an IMW. As it is a single-center study, it does not allow the generalization of the results obtained; however, this study is important for to alert all doctors and other health professionals to *delirium*, its value and need of recognition, impact on these wards, and to improve clinical practice and patient care.

The author highlight the need to train professionals to improve the recognition and prevention of *delirium* through multidisciplinary approaches with optimization of non-pharmacological measures and pharmacological restraint, in order to avoid physical one, and reduce the negative consequences of this entity on the patient, family and health professionals.

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## CONCLUSION

*Delirium* is frequent and has a high impact on the IMW, whose population is particularly susceptible due to marked aging, with inherent multimorbidity and fragility. The systematic use of screening and diagnostic scales increases the early identification of *delirium*, allowing to reduce its consequences, particularly in terms of mortality, becoming urgent to change and improve incorrect practices.

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