ORIGINAL ARTICLE

Delirium symptoms duration and mortality in SARS-COV2 elderly: results of a multicenter retrospective cohort study

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Abstract

Background Since the occurrence of the SARS-COV2 pandemic, there has been an increasing interest in investigating the epidemiology of delirium. Delirium is frequent in SARS-COV2 patients and it is associated with increased mortality; however, no information is available on the association between delirium duration in SARS-COV2 patients and related outcomes.

Aims The aim of this study is to investigate the association between the duration of delirium symptoms and in-hospital mortality in older patients with SARS-COV2 infection.

Methods Retrospective cohort study of patients 65 years of age and older with SARS-CoV 2 infection admitted to two acute geriatric wards and one rehabilitation ward. Delirium symptoms duration was assessed retrospectively with a chart-based validated method. In-hospital mortality was ascertained via medical records.

Results A total of 241 patients were included. The prevalence of delirium on admission was 16%. The median number of days with delirium symptoms was 4 (IQR 2–6.5) vs. 0 (IQR 0–2) in patients with and without delirium on admission. In the multivariable Cox regression model, each day with a delirium symptom in a patient with the same length of stay was associated with a 10% increase in in-hospital mortality (Hazard ratio 1.1, 95% Confidence interval 1.01–1.2; $p = 0.03$). Other variables associated with increased risk of in-hospital death were age, comorbidity, CPAP, CRP levels and total number of drugs on admission.

Conclusions The study supports the necessity to establish protocols for the monitoring and management of delirium during emergency conditions to allow an appropriate care for older patients.

Keywords COVID · SARS-COV2 · Elderly · Delirium · Delirium symptoms

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Introduction

Delirium is a serious neuropsychiatric condition characterized by acute onset, inattention, fluctuation along with other cognitive deficits and it is usually caused by a medical condition [1]. The cause of delirium is often multifactorial (e.g., infections, change in medications, use of restraints) especially in older patients [2]. In late 2019, a new emerging risk factor for delirium was the infection with SARS-COV2 [3]. The main hypothesis of the pathogenesis of delirium in patients with SARS-COV2 is a central neuroinflammation along with the worsening of other geriatric syndromes, which can be worsened by the infection itself or by the acute isolation related to the health care policies to reduce the spread of the viral infection [3].

It is known that delirium is frequent in older patients and its prevalence is reported between 11 and 42% in acute hospitals [2, 4, 5]. Delirium is associated with worse outcomes including longer hospital stay, increased mortality, health care costs, worsening of functional and cognitive status, and increased risk of dementia [2, 5, 6]. Delirium is also associated with patients' and caregivers' distress [7]. Importantly, researches have also shown how the duration of delirium further worsens its effects. Indeed each single day of delirium has been shown to be associated with a 10–15% increase in mortality at 6 months and at 1 year [8–10].

Since the occurrence of the SARS-COV2 pandemic, there has been an increasing interest in investigating the epidemiology of delirium. A recent review has reported how delirium affects up to 80% of the patients with SARS-COV2 in the ICU and between 29 and 67% in non-ICU patients [3]. Delirium in patients with SARS-COV2 is reported to increase the risk of mortality and worsen patients' functional outcomes [11, 12]. However, there are no information on the effect of delirium duration on patient's health status. The assessment of delirium during the SARS-COV2 emergency has been difficult in many medical wards due to the overwhelming management of acute patients. A possible approach to investigate the duration of delirium and delirium symptoms is to retrospectively analyze medical chart for the presence of delirium symptoms, as previously described [13].

The aim of this study is to investigate the association between the duration of delirium symptoms and in-hospital mortality in older patients with SARS-COV2 infection.

Methods

Study population

This was a retrospective cohort study of patients 65 years of age and older with SARS-CoV-2 infection (positive result by SARS-CoV-2 nasopharyngeal swab polymerase chain reaction test) admitted to two acute geriatric wards of tertiary hospitals (San Gerardo hospital, in Monza and Città della Salute e della Scienza, Molinette Hospital, Torino) and one rehabilitation ward of a private hospital (Fondazione Teresa Camplani, Cremona) in Italy from February 22, 2020 to May 17, 2020.

Patients were admitted to the acute ward from the emergency department or transferred from acute hospital wards in those admitted to the rehabilitation ward. Exclusion criteria were an age younger than 65 years of age and the refusal of giving verbal consent by the patient or by a proxy on admission. The study protocol was approved by the Brianza Institutional Review Board (protocol n. 2572).

Assessment of delirium and delirium symptoms duration

The presence of delirium on admission was ascertained either by the presence of a formal assessment with the 4AT [14] or via a chart-based validated method. The 4AT was originally validated in acute geriatric wards and rehabilitation wards [14]. A recent systematic review and meta-analysis reported high sensitivity (0.88, 95% CI 0.80–0.93) and specificity (0.88, 95% CI 0.82–0.92) of the 4AT for the assessment of delirium [15].

Delirium symptoms duration was assessed retrospectively with a chart-based validated Method [13] also used in other studies for this purpose [16, 17]. Each patient's chart was retrospectively reviewed for the daily presence of ten key words (i.e., confusion, disorientation, altered mental status, delirium, agitation, inappropriate behavior, mental status change, inattention, hallucination, lethargy). The source of information of the key words were medical, nurses, physical therapists' notes. The medical records were reviewed until patient's discharge or death or up to a maximum of 45 days. The duration of delirium symptoms was then defined according to the presence of any of the key words on each day during the hospital stay.

Study outcomes

The primary end-point was in-hospital mortality assessed through medical records.

Data collection and clinical assessment

We recorded on admission the following variables: demographics, smoking status, comorbidities (i.e., cardiac disease, hypertension, diabetes mellitus, chronic obstructive pulmonary disease—COPD, dementia), malnutrition assessed clinically, and the total number of medications. The functional status was evaluated differently in the acute geriatric wards using two items of the Katz's Activities of Daily Living (ADLs) (i.e., ability in self-bathing and self-dressing) and in the rehabilitation wards with the Barthel Index. Therefore, we created a new variable to assess patient's disability according to the presence of dependency in self-bathing or self-dressing or to a Barthel Index score ≤ 90/100 with reference to one month before the hospitalization for SARS-COV2 infection [11].

We recorded on admission laboratory exams (white blood cell count; C-reactive protein, CRP; albumin), the use of oxygen and continuous positive airway pressure

(CPAP) for respiratory support, the presence and the degree of chest infiltrates on chest X-ray or CT scan.

Statistical analysis

Continuous variables were described with median and inter-quartile range (IQR), and categorical data were expressed as frequency and percentage. Clinical features of the patients with and without delirium on admission were compared by Mann–Whitney test and Fisher test for continuous and categorical data, respectively.

The percentage of days with delirium symptoms was computed for each patient as the total number of days with delirium symptoms divided by the total number of days in the ward. The distribution of the percentage of days was reported by a violin plot (kernel density) over-imposed on a box-plot by in-hospital discharge status (dead, alive).

To evaluate the association between the percentage of days with delirium symptoms during hospital stay and in-hospital mortality we applied a time-dependent multivariable Cox regression model stratified for center, in which the variable number of days with delirium is updated every day according to delirium status by a cumulative sum. The percentage of delirium days was computed as the number of delirium days divided by the length of stay to standardize for length of stay that could indeed be influenced by many factors, including delirium. The time-dependent Cox model adjusts for this potential bias by considering the number of patients at risk each day. The time origin is the day of ward's admission and patient is followed up to death or discharge, whichever occurs first. Patients transferred in other wards were followed up to hospital discharge but on the purpose of this analysis were censored at transfer. The model included potential confounders selected by generalized linear model with lasso penalty: sex, age, number of chronic diseases, cardiac disease, COPD, use of CPAP, number of chronic drugs, chest X-ray or CT, CRP serum levels. The shrinkage parameter was set as the one minimizing the mean prediction error by a tenfold cross validation. Proportional hazard assumption was fulfilled. Results were obtained using SAS (version 9.4) and R software (version 3.5.2).

Results

A total of 241 patients were included, 203 admitted to acute geriatric wards, and 38 to a rehabilitation ward.

The prevalence of delirium on admission was $39/241 = 16\%$. Patients with delirium on admission were older, with higher number of comorbidities and higher prevalence of dementia. Functional disability, before the index admission, was higher in patients with delirium (Table 1).

Overall, we observed a total number of days with delirium symptoms of 566 out of 3886 hospitalization days: thus, days with delirium were 15% of total days of hospitalization. The median number of days with delirium symptoms was higher in subjects with delirium at admission (4, IQR 2–6.5, vs. 0, IQR 0–2). In patients with delirium at admission, the median percentage of days of delirium symptoms per days of hospital stay was 50% (IQR 6.3–67.3%).

A total of 77 in-hospital deaths were observed, 20 (51%) in patients with delirium at admission and 57 (28%) in the others ($p = 0.008$). Patients who died in the hospital were older, with higher prevalence of malnutrition, smoking history, dementia, functional disability, cardiac disease and overall a higher number of comorbidities and medications (Table 2). Likewise, the degree of the infection was more severe in patients who died than in the others, as indicated by a higher prevalence of single or bilateral lung opacities and by the need of Oxygen support or CPAP use. The median number of delirium symptoms days in those who died was 2 (IQR 0.0–4.0) and the percentage of days of delirium symptoms per days of hospital stay was 22 (IQR 0.0–60). Figure 1 shows the distribution of the percentage of days with delirium symptoms according to in-hospital mortality, showing that the majority of alive patients did not show any delirium symptoms during hospital stay, while patients who died had higher percentage of days with delirium symptoms.

In the multivariable Cox regression model, each day with a delirium symptom in a patient with the same length of stay was associated with a 10% increase in in-hospital mortality (Hazard ratio 1.1, 95% confidence interval 1.01–1.2; $p = 0.03$). Other variables associated with increased risk of in-hospital death were age (HR 1.03, 95% CI 1–1.06; $p = 0.05$), comorbidity (HR 1.3, 95% CI 1.03–1.5; $p = 0.025$), CPAP (HR 2.11, 95% CI 1.11–4.02; $p = 0.02$), CRP levels (HR 1.08, 95% CI 1.04–1.12; $p < 0.001$) and total number of drugs (HR 1.13, 95% CI 1.04–1.23; $p = p < 0.001$) on admission (Table 3).

Discussion

The study confirms previous data on the prevalence of delirium on admission in acutely ill older patients and provides new information on the duration of delirium symptoms. Forty nine percent of the patients experienced at least 1 day with delirium symptoms and each day with a delirium symptom in a patient with the same length of stay was associated with a 10% increase in in-hospital mortality.

Previous studies have reported delirium prevalence in non-ICU SARS-COV2 patients between 29 and 67% [3]. In this population, it was confirmed that delirium on admission is associated with increased mortality and length of hospital stay. [3, 11, 18] A large Italian multicenter study showed that

Table 1 Patients' characteristics by delirium at admission

Variable*	Entire sample	No delirium $N=202$	Delirium $N=39$	p value	Missing%
Age	77.5 [65.6, 85.0]	76.8 [64.5, 84.1]	83.3 [79.1, 87.6]	0.001	0
Gender (male), N (%)	143 (59)	125 (62)	18 (46)	0.076	0
Smoking (current or previous), N (%)	61 (35)	53 (34)	8 (38)	0.808	27
Cardiac diseases, N (%)**	93 (39)	75 (37)	18 (46)	0.369	0
Hypertension, N (%)	143 (59)	118 (58)	25 (64)	0.595	0
Diabetes mellitus, N (%)	57 (24)	43 (21)	14 (36)	0.063	0
COPD, N (%)	27 (11)	21 (10)	6 (15)	0.404	0
Dementia, N (%)	42 (17)	23 (11)	19 (49)	<0.001	0
Number of chronic diseases (excluding dementia)	2.0 [1.0, 3.0]	2.0 [1.0, 3.0]	3.0 [2.0, 4.0]	0.008	0
Malnutrition	74 (35)	58 (32)	16 (50)	0.069	12
Number of medications on admission	6.0 [2.0, 8.0]	5.0 [2.0, 8.0]	6.0 [4.0, 8.0]	0.134	0.8
Functional disability, N (%)***	98 (42)	70 (35)	28 (74)	<0.001	2.1
Chest X-ray or CT results, N (%)				0.586	0
No opacity	33 (14)	29 (14)	4 (10)		
Single opacity	134 (56)	109 (54)	25 (64)		
Multiple or bilateral opacities	74 (31)	64 (32)	10 (26)		
CPAP on admission	30 (12)	25 (12)	5 (13)	1	0
Laboratory indicators					
White blood cell count ($\times 10^9$/l)	6.2 [4.7, 9.2]	6.2 [4.8, 9.2]	6.1 [4.6, 10.2]	0.945	0.4
c-reactive protein, mg/dl	4.9 [1.6, 8.9]	4.9 [1.4, 8.7]	4.5 [2.1, 10.9]	0.343	0.4
Albumin gr/dl	3.2 [2.8, 3.6]	3.3 [2.8, 3.6]	3.2 [3.0, 3.5]	0.782	56
Days of delirium symptoms	0.0 [0.0, 3.0]	0.0 [0.0, 2.0]	4.0 [2.0, 6.5]	<0.001	0
Length of stay (days)	12.0 [7.0, 22.0]	12.0 [7.0, 22.0]	13.0 [7.0, 19.0]	0.603	0
Percentage of days of delirium symptoms/days of hospital stay	0.0 [0.0, 23.5]	0.0 [0.0, 16.3]	50.0 [6.3, 67.3]	<0.001	0
Mortality	77 (32)	57 (28)	20 (51)	0.008	0

CPAP: Continuous positive airway pressure; COPD: chronic obstructive pulmonary disease

*Median [IQR] where not otherwise specified

**Cardiac diseases included congestive heart failure, coronary heart diseases and atrial fibrillation

*** Functional disability was defined according to the presence of dependency in self-bathing or self-dressing or with a Barthel Index score ≤ 90/100 one month before the index hospitalization

delirium on admission was associated with almost a twofold increase in the risk of in-hospital mortality [11]. In the last years, researchers have further investigated how delirium is associated with worse outcomes not only when considered as a single episode but even more when the severity and the duration of delirium is measured [8–10]. Indeed several studies have emphasized the importance of delirium monitoring with validated tools not only at the time of admission to a single setting but also on a daily basis, since each day of delirium increases the risk of mortality by 10–17% [8–10].

Given the difficulties in spreading the practice of delirium monitoring in the daily routine, researchers have also investigated the possibility to detect delirium symptoms using a validated method in geriatric and medical wards [13]. This method has been applied also in postacute care and pulmonary wards [16, 17]. Using this method, the prevalence of delirium symptoms in patients with severe pneumonia was

31% and the presence of at least one delirium symptoms during the hospitalization was associated with a more than twofold increase in the odds of one-year mortality [17]. In our study, we found a significant association between the duration of delirium symptoms and in-hospital mortality in older patients with SARS-COV2 infection. These findings support previous investigations reporting the association between delirium duration and increased mortality [8–10].

The emergency related to the SARS-COV2 pandemic has determined a rapid subversion of the health care system organization, which, of course, did not spare the geriatric wards. Usually, a patient admitted to a geriatric ward is evaluated with a comprehensive geriatric assessment including delirium evaluation using validated tools such as the Confusion Assessment Method (CAM) [19] or the 4AT [14]. With the SARS-COV2 emergency, medical staffs were profoundly redesigned and specialists with a different

Table 2 Patients' characteristics according to in-hospital death

Variable*	Alive N = 164	Dead N = 77	*p* value	Missing (%)
Age (years)	74.4 [62.1, 83.0]	83.3 [76.9, 89.0]	< 0.001	0
Gender (male), *N* (%)	91 (55)	52 (68)	0.092	0
Smoking (current or previous), *N* (%)	36 (29)	25 (47)	0.026	27
Cardiac diseases, *N* (%)**	47 (29)	46 (60)	< 0.001	0
Hypertension, *N* (%)	89 (54)	54 (70)	0.024	0
Diabetes mellitus, *N* (%)	33 (20)	24 (31)	0.074	0
COPD, *N* (%)	15 (9)	12 (16)	0.187	0
Dementia, *N* (%)	21 (13)	21 (27)	0.01	0
Number of chronic diseases (excluding dementia)	2.0 [1.0, 3.0]	3.0 [2.0, 4.0]	< 0.001	0
Malnutrition, *N* (%)	39 (27)	35 (53)	< 0.001	12
Number of medications on admission	4.0 [1.0, 7.0]	7.0 [5.0, 9.5]	< 0.001	0.8
Functional disability, *N* (%)***	53 (33)	45 (61)	< 0.001	2.1
Chest X-ray or CT results, *N* (%)			0.005	0
No opacity	30 (18)	3 (4)		
Single opacity	84 (51)	50 (65)		
Multiple or bilateral opacities	50 (30)	24 (31)		
CPAP on admission, *N* (%)	13 (10)	14 (20)	0.001	
Laboratory indicators (median [iqr])				
White blood cell count ($\times 10^9$/l)	5.8 [4.6, 8.3]	6.9 [5.2, 10.8]	0.006	0.4
c-reactive protein, mg/dl	3.4 [1.1, 7.6]	8.0 [4.3, 14.6]	< 0.001	0.4
Albumin gr/dl	3.2 [2.8, 3.6]	3.3 [3.0, 3.5]	0.845	56
Delirium on admission, *N* (%)	19 (12)	20 (26)	0.007	0
Days of delirium symptoms	0.0 [0.0, 2.0]	2.0 [0.0, 4.0]	< 0.001	0
Percentage of days of delirium symptoms/days of hospital stay	0.0 [0.0, 7.7]	22.2 [0.0, 60.0]	< 0.001	0
Length of stay (days)	14.0 [8.0, 25.2]	7.0 [5.0, 13.0]	< 0.001	0

CPAP: Continuous positive airway pressure, COPD: chronic obstructive pulmonary disease

*Median [IQR] where not otherwise specified

**Cardiac diseases included congestive heart failure, coronary heart diseases and atrial fibrillation

***Disability was defined according to the presence of dependency in self-bathing or self- dressing or with a Barthel Index score ≤ 90/100 1 month before the index hospitalization

background were added to the staff and called to comply with practices which are not typical of their expertise, such as delirium assessment. This change in the organization did not allow to always ensure the optimal approach to geriatric patients. Additionally, older patients are managed with protocols to prevent and treat delirium with an interdisciplinary and multidisciplinary approach [20]. Delirium assessment and prevention have been deeply affected, with obvious consequences in delirium management.

The study findings of an association between delirium symptoms and mortality should prompt clinicians and health care policy makers to consider how to approach the care of geriatric patients during an emergency, keeping the cardinal geriatric evaluations as to allow an adequate care. Within these evaluations, delirium monitoring should not be forgotten. One should be aware that tools such as the CAM or the 4AT might be difficult to be used during emergency

situation and other screening tools for delirium can be used. For instance, the modified Richmond Agitation and Sedation Scale (m-RASS) [21] has been shown to have high specificity in delirium detection even in busy settings (i.e., emergency departments) and in patients with dementia [22]. The abnormal arousal level, as measured with the m-RASS, has also been shown to be associated with increased mortality at 1-month and 6-month follow-up [23]. The m-RASS has the advantage to be easy to use at the bedside and does not required a specific training allowing a daily monitoring of the possible presence of delirium.

Our study presents strengths along with limitations. This is the first multicenter study to report the association between delirium symptoms and in-hospital mortality in a relatively large cohort of elderly patients with SARS-COV2. In the current study, we used a previously validated methods for the detection of delirium symptoms via the review of

Fig. 1 Violin plot and box-plot on the distribution of the percentage of days with delirium symptoms on hospital stay by in-hospital discharge status (dead, alive). Colored areas reports the kernel density in alive subjects (gray) and dead (orange). Box represents first and third quartile and the inner line indicates the median; the whiskers are located at the maximum and minimum observation (outside observations indicated with dots are those out of the 1.5 × interquartile range). The figures shows that the majority of alive patients did not show any delirium symptoms during hospital stay, while patients who died had higher percentage of days with delirium symptoms
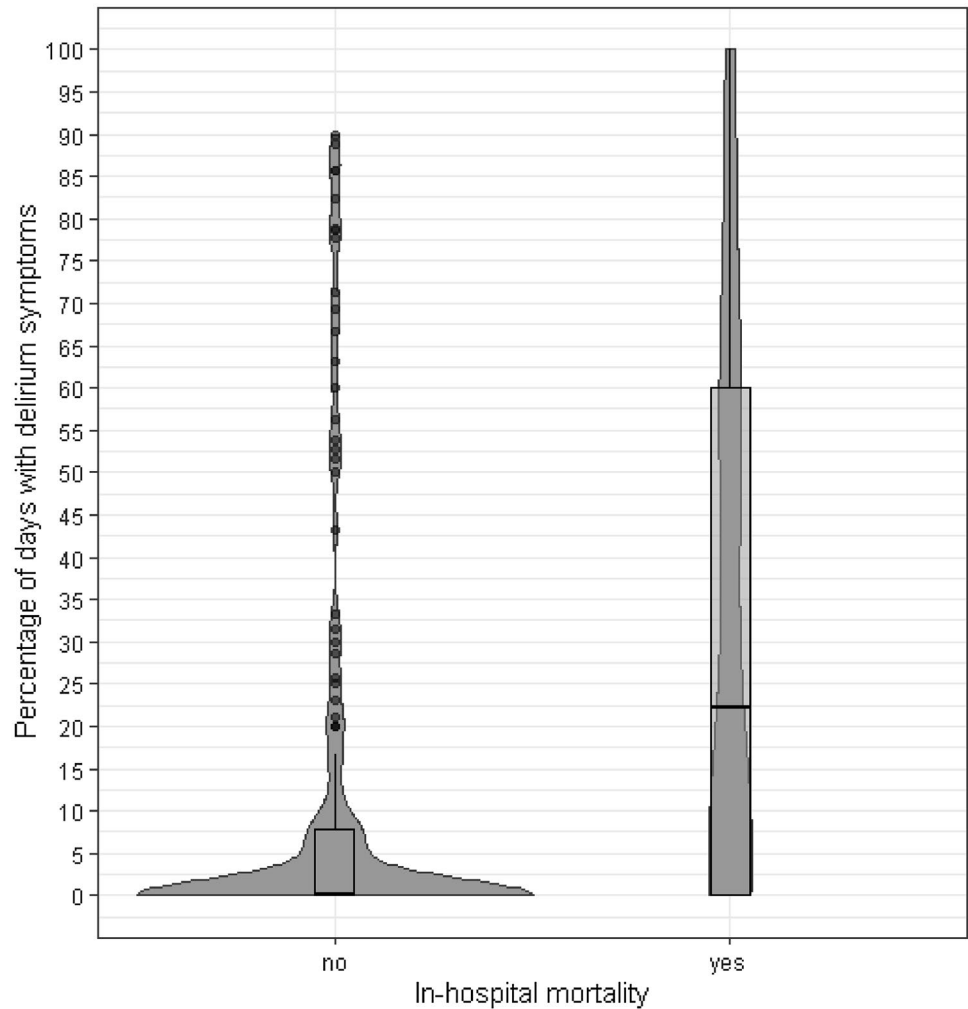
Table 3 Time-dependent multivariable Cox regression model stratified for center on the association between days of delirium symptoms and in-hospital mortality (238 patients, 68 events)

	HR (95% CI)	*p*
Days of delirium symptoms	1.10 (1.01;1.2)	0.0346
Gender (male)	1.63 (0.89;3.00)	0.1133
Age	1.03 (1.00;1.06)	0.0524
Comorbidity	1.24 (1.03;1.50)	0.0258
Cardiac disease*	1.30 (0.71;2.38)	0.3984
COPD	0.80 (0.39;1.65)	0.5443
CPAP on admission	2.11 (1.11;4.02)	0.0229
Number of medications on admission	1.13 (1.04;1.23)	0.0034
Bilateral lung opacity on admission	3.05 (0.87;10.68)	0.081
Single lung opacity on admission	3.07 (0.86;11.00)	0.085
CRP on admission	1.08 (1.04;1.12)	0.0001

COPD: Chronic obstructive pulmonary disease; CPAP: Continuous positive airway pressure; CRP: C-reactive protein; HR: hazard ratio; CI: confidence interval

*Cardiac diseases included congestive heart failure, coronary heart diseases and atrial fibrillation

medical records. The limitations include the retrospective design of the study and a non-formal assessment of delirium on daily basis with validated methods such as the CAM or the 4AT. However, this approach in an emergency situation allowed us to obtain results that are consistent with previous studies.

Conclusions

The duration of delirium symptoms in older patients with SARS-COV2 infection was found to be associated with a significant increase in in-hospital mortality. The study supports the necessity to establish protocols for the monitoring and management of delirium during emergency conditions to allow an appropriate care for older patients.

Declarations

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