Prevalence and risk factors associated with *delirium* at a critical care unit

Prevalência e fatores de risco associados ao *delirium* em uma unidade de terapia intensiva

Prevalencia y factores de riesgo asociados al *delirium* en una unidad de cuidados intensivos

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Abstract

Objective: Identify the prevalence and risk factors associated with *delirium* in patients in a critical care unit in northeastern Brazil.

Methods: A cross-sectional study that enrolled 316 patients with at least 48h of hospitalization, ≥18 years old, with Richmond Agitation-Sedation Scale ≥ -3, between July 2017 and April 2018. Statistical analysis included univariate and multivariate analysis, we employed a log-binomial model for adjusted prevalence ratios.

Results: Univariate analysis indicated that *delirium* was prevalent among 45.9%, middle age (49.8 ± 17.4 vs. 44.0 ± 17.6, p=0.003) and neurosurgery (62.5% vs. 26.1%, p<0.001). Physical restraining (81.3% vs. 40.9%, p<0.001), nasoenteral tube feeding (85.9% vs. 57.6%, p<0.001) and mechanical ventilation (50.0% vs. 29.2%, p<0.001) was associated with prevalence of *delirium*.

Conclusion: Age, physical restraint, tube feeding, and the use of anticonvulsants increase the prevalence of *delirium* in our sample.

Resumo

Objetivo: Identificar a prevalência e os fatores de risco associados ao *delirium* em pacientes internados em uma unidade de terapia intensiva no nordeste do Brasil.

Métodos: Estudo transversal realizado entre julho de 2017 e abril de 2018 com 316 pacientes hospitalizados por pelo menos 48h, ≥18 anos, com Richmond Agitation-Sedation Scale ≥ -3. A análise estatística incluiu análise univariada e multivariada; um modelo log-binomial foi utilizado para razões de prevalência ajustadas.

Resultados: A análise univariada indicou uma prevalência de *delirium* em 45,9%, meia idade (49,8 ± 17,4 vs. 44,0 ± 17,6, p=0,003) e neurocirurgia (62,5% vs. 26,1%, p<0,001). A contenção física (81,3% vs. 40,9%, p<0,001), alimentação por sonda nasoenteral (85,9% vs. 57,6%, p<0,001) e ventilação mecânica (50,0% vs. 29,2%, p<0,001) foram associadas à prevalência de *delirium.*

Conclusão: Idade, contenção física, alimentação por sonda e uso de anticonvulsivantes aumentaram a prevalência de *delirium* em nossa amostra.

Resumen

Objetivo: Identificar la prevalencia y los factores de riesgo asociados al *delirium* en pacientes internados en una unidad de cuidados intensivos en el nordeste de Brasil.

Métodos: Estudio transversal realizado entre julio de 2017 y abril de 2018 con 316 pacientes hospitalizados por al menos 48 horas, ≥18 años, con Richmond Agitation-Sedation Scale ≥ -3. El análisis estadístico incluyó

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análisis univariado y multivariado. Se utilizó un modelo log-binomial para razones de prevalencia ajustadas.

Resultados: El análisis univariado indicó una prevalencia de *delirium* en el 45,9 %, mediana edad (49,8 ± 17,4 vs. 44,0 ± 17,6, p=0,003) y neurocirugía (62,5 % vs. 26,1 %, p<0,001). La contención física (81,3 % vs. 40,9 %, p<0,001), alimentación por sonda nasoenteral (85,9 % vs. 57,6 %, p<0,001) y ventilación mecánica (50,0 % vs. 29,2 %, p<0,001) fueron factores asociados a la prevalencia de *delirium*.

Conclusión: Edad, contención física, alimentación por sonda y uso de anticonvulsivos aumentaron la prevalencia de *delirium* en nuestra muestra.

Introduction

Delirium has a quick onset in the intensive care unit (ICU).[1] It may affect older and frail patients with functional disability and dementia.[2] Patients with *delirium* receive more sedation and higher doses of drugs such as midazolam and fentanyl, as well as continuous infusions of dexmedetomidine, propofol, and fentanyl.[3]

As a consequence, *delirium* worsens clinical conditions, increases the need for care, prolongs hospitalization, and increases mortality risk.[4] Furthermore, *delirium* is associated with age and gender-specific frailty, medical condition, and dementia.[5] A cohort study estimated that cumulative costs for *delirium* treatment over 30 days ranged from $11,132 to $23,497[6] dollars. A meta-analysis[7] identified that prevalence of *delirium* associates with worse clinical outcomes and occurrence of adverse events.[8]

Delirium in ICU can be considered a critical problem based on its prevalence, cost, and negative impacts on patients' quality of life, calling for interventions for treatment and prevention based on its risk factors. Among risk factors, the non-modifiable risk factors associated with *delirium* in the ICU include age, dementia, and stroke. Potentially modifiable factors involve pharmacological treatment with benzodiazepine, opioids, sedatives, analgesic, hypoxemia, metabolic disorders, and severity of illness.[9,10] Finally, modifiable factors include isolation, excessive use of technology, equipment, changes in sleep and wakefulness,[9] physical restraint, and the use of enteral nutrition, urinary catheters, and central venous catheters.[10]

Interventions focused on modifiable risk factors may ensure patients' health outcomes in clinical practice. However, existing guidelines for prevention and treatment of *delirium* are non-specific, providing limited guidance for pain, agitation, sedation, immobility, and disturbed sleep in ICU patients. Furhermore, there is a gap in the evidence between theoretical guidance and clinical practice; thus, the absence of specific guidelines along with a wide variety of therapeutic arsenal lead to a lack of consensus in treatment.[11]

This study aims to identify the prevalence and risk factors associated with *delirium* among patients in a critical care unit in northeastern Brazil.

Methods

Population and sample characterization

Hospitalized patients aged 18 years or older, admited for at least 48h at medical and surgical intensive care units (ICU) at the Sergipe Emergency Hospital (HUSE) in the state of Sergipe, northeastern Brazil, were enrolled in an observational cross-sectional study between August 2017 and October 2018. The ICU has a functional capacity of fifty-four beds.

The sample size was calculated considering the *delirium* outcome based on the multicenter study by Salluh et al. (2010)[8] developed in intensive care units in South America (Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Peru, and Uruguay); North America (Mexico and the United States) and Europe (Spain), in which the prevalence of *delirium* was 32.3%. A prevalence of at least 28% was assumed. Pocock's[12] calculation was used, and an expected error of 5% was assumed. The calculation yield a sample size of 310 patients.

Patients with at least 48h of hospitalization, at 18 years old or older, sedated or weaned, with Richmond Agitation-Sedation Scale (RASS) ≥ -3 (moderate sedation with eye movement or opening of the eyes) were included. Critically ill patients with a Glasgow score ≤8, aphasia, brain death, or who were in custody were excluded. This study was

approved by the Ethics Committee of the Federal University of Sergipe on May 8th, 2017, under opinion number 2.051.128.

Variables and Data collection

Predisposing and precipitating risk factors for *delirium* included sociodemographic data, gender, age, medical diagnosis according to ICU admission, cause of hospitalization, medical history, smoking, alcohol consumption, visual impairment, history of depression, dementia, heart failure, stroke, epilepsy, kidney disease, liver disease, HIV infection, the use of psychotropic drugs, malnutrition, and hypertension. Data collection of precipitants factors related to current hospitalization included RASS Scale Score,[13] dehydration, hydro electrolytic disorder, glycemic alteration, high blood pressure, hypothermia, fever, hypoxemia, immobility, physical restraint, tube feeding, mechanical ventilation, central venous catheter, and urinary catheter, and the Prognostic Comorbidity Index of Charlson.[14] The Glasgow Coma Scale (GCS) was used to evaluate consciousness in comatose patients with traumatic brain injury (TBI) and classified in mild (GCS 13 to 15), moderate (GCS 9 to 12), or severe GCS ≤ 8.[15]

Delirium assessment

The Confusion Assessment Method in an Intensive Care Unit (CAM-ICU)[1,16] was used to assess *delirium*. All assessments were performed by a team of volunteer nurses and undergraduate nursing and medical students previously trained in the RASS, GCS, CAM-ICU evaluation, and secondary data handling. Data were collected in two stages. First, we evaluated patients sedated or awake with the RASS scale and comatose patients with the CGS scale. In the second stage, CAM-ICU was implemented. All data were retrieved from the medical records at the time of enrollment in the study, and all scales results were included in medical records.

Data analysis

We described categorical variables with absolute frequency and relative percentage and continuous variables with mean and standard deviation. Exact Tests of Fisher, Pearson's Chi-Square, and Pearson Chi-Square with Monte-Carlo simulations were used for testing associations between categorical variables. The Shapiro-Wilk was used for testing continuous variables adherence to normal distribution. *T*-test for independent samples or Mann-Whitney tests were used for evaluating differences in continuous variables. Crude prevalence ratios were estimated and adjusted by log-binomial regression and the Backward Selection method for variable selection with an input significance of 10%. In all analyses, only valid observations were considered. We adopted 5% as the significance level and used the R Core Team 2019 software for all the analyses.

Results

Eight hundred and thirty-five patients were screened, and 316 met the inclusion criteria. *Delirium* was prevalent among 45.9% of subjects. Participants were categorized into two groups according to the presence or absence of *delirium*. Association between *delirium*, medical, and demographic variables is described in table 1. The prevalence of middle age (49.8 ± 17.4 *vs.* 44.0 ± 17.6, p=0.003) and neurosurgery (62.5% vs 26.1%, p<0.001) was significantly higher in the *delirium* group.

Among factors associated with *delirium,* a univariate analysis yield higher frequency of patients in physical restraint (81.3% vs. 40.9%, p<0.001), nasoenteral tube feeding (85.9% vs. 57.6%, p<0.001), and in use of mechanical ventilation (50.0% vs. 29.2%, p<0.001) in the group with *delirium* when compared to those in the group without it. In addition, patients with *delirium* had a higher incidence of pressure ulcer (33.3% vs. 189%, p=0.004), received more fentanyl as sedative (24.8% vs. 8.2%, p<0.001), more muscle relaxants, (4.8% vs 0.6%, p=0.027) and required more vasopressor (9.0% vs. 2.9%, p=0.021) and anticonvulsants (35.2% vs. 19.9%, p=0.002) medications when compared to those without *delirium* (Table 2).

We estimated crude prevalence ratios from 10% significant variables in univariate analysis,

Table 1. Clinical and demographic characterization according to the occurrence of *delirium*

Variables	CAM-ICU		p-value
	CAM-ICU + With *delirium* (n = 145) n(%)	CAM-ICU - Without *delirium* (n = 171) n(%)	
Age, *mean* (SD‡)	49.8(17.4)	44.0(17.6)	0.003 [WII]
Gender, n*(%)†			
Male	100(69)	110(64.3)	0.384 [QI¶]
Female	45(31)	61(35.7)	
Residency, n*(%)†			
Sergipe town other than Aracaju	77(53.1)	100(58.5)	
Aracaju	65(44.8)	67(39.2)	0.614 [QM**]
Other states	3(2.1)	4(2.3)	
Co-morbidity			
High blood pressure, n*(%)†	26(52)	30(49.2)	0.768 [QI¶]
Diabetes, n*(%)†	18(36)	14(23)	0.146 [F††]
Reason for ICU admission, n*(%)†			
Injury, poisoning, and others	64(44.1)	61(35.7)	0.170 [QI¶]
Cardiovascular disease	19(13.1)	18(10.5)	
Digestive tract disease	12(8.3)	25(14.6)	
Admission origin, n*(%)†			
Emergency	107(74.3)	111(64.9)	0.312 [QM**]
Surgical Ward	25(17.4)	37(21.6)	
Clinical Ward	9(6.3)	17(9.9)	
Others	3(2.1)	6(3.5)	
Hospitalization type, n*(%)†			
Clinical	78(54.5)	79(47)	0.374 [QM**]
Surgical/emergency surgery	61(42.7)	81(48.2)	
Reason of Clinical Hospitalization, n*(%)†			
Neurological	23(28.4)	11(12.9)	
Sepsis	22(27.2)	24(28.2)	0.241 [QM**]
Trauma	10(12.3)	13(15.3)	
Renal	7(8.6)	8(9.4)	
Respiratory Failure (except sepsis)	5(6.2)	4(4.7)	
Digestive	5(6.2)	10(11.8)	
Other	9(11.1)	15(17.6)	
Reason for Surgical Hospitalization, n*(%†)			
Neurosurgery	45(62.5)	24(26.1)	<0.001 [QM**]
Abdominal surgery	17(23.6)	36(39.1)	
Other surgery	10(13.9)	32(34.8)	

*n - absolute frequency; †% relative percentage frequency; ‡SD - Standard Deviation; [IIW] - Mann-Whitney Test; [¶Q] - Pearson's Chi-Square Test; **[QM]- Pearson Chi-Square Test with Monte Carlo simulations; ††[F] - Fisher's Exact Test

attempting to create multiple models for *delirium*. We observed that higher crude prevalence ratios in *delirium* were linked to age, surgical approach by neurosurgery, physical restrainment, enteral tube feeding, use of mechanical ventilation, presence of pressure ulcer, use of fentanyl, anticonvulsant, and muscle relaxants. In multiple models, we observed higher prevalence ratios for *delirium* by age, physical restrainment, enteral tube feeding, anticonvulsant, and muscle relaxants (Table 3).

Table 2. Clinical and hospitalization characterization according to the occurrence of delirium

Characteristics	CAM-ICU		p-value
	CAM-ICU + With *delirium* (n = 145) n(%)	CAM-ICU - Without *delirium* (n = 171) n(%)	
Physical Restraint, n*(%)†	117(81.3)	70(40.9)	<0.001 [QII]
Tube feeding, n (%)	122(85.9)	98(57.6)	<0.001 [QII]
Mechanical ventilation, n*(%)†	72(50.0)	50(29.2)	<0.001 [QII]
Device for MV, n*(%)†			
TOT	41(56.2)	31(63.3)	0.434 [QII]
TQT	32(43.8)	18(36.7)	
Devices for health assistance			
Vesical Cathether, n*(%)†	78(55.7)	98(58.3)	0.644 [QII]
Pressure ulcer n*(%)†	47(33.3)	31(18.9)	0.004 [QII]
Central Venous Access, n*(%)†	82(57.7)	96(58.5)	0.889 [QII]
ECG/RASS, n*(%)†			
GCS/ TBI	78(54.2)	112(65.5)	0.041 [QII]
RASS	73(53.7)	63(46.3)	
CHALRSON, mean (SD‡)	1.7(1.9)	1.8(2.6)	0.336 [W¶]
Sedation			
Fentanyl, n*(%)†	36(24.8)	14(8.2)	<0.001 [F††]
Vasoactive drugs			
Noradrenaline, n*(%)†	13(9.0)	5(2.9)	0.021 [F††]
Nitroglycerin, n*(%)†	2(1.4)	7(4.1)	0.148 [F††]
Other medication			
Anticonvulsants, n*(%)†	51(35.2)	34(19.9)	0.002 [QII]
Muscle Relaxants, n*(%)†	7(4.8)	1(0.6)	0.027 [F††]
Death, n*(%)†	36(54.5)	30(45.5)	0.112 [QII]

*n - absolute frequency; †% relative percentage frequency; ‡SD - Standard Deviation; [IIQ] - Pearson's Chi-Square Test; [¶W] - Mann-Whitney Test; [F] - Fisher's Exact Test

Table 3. Log-binomial regression analysis of variables associated with *delirium*

Variables	CAM-ICU		p-value
	PR* (CI95%)	PRa† (CI95%)‡	
Age	1.01 (1.00-1.02)	1.01 (1.00-1.01)	0.010
Reason for surgical hospitalization			
Neurosurgery	2.74 (1.55-4.83)		
Abdominal surgery	1.35 (0.69-2.63)		
Other surgery	1		
Physical Restraint	3.00 (2.08-4.22)	2.12 (1.42-3.15)	<0.001
Tube feeding	2.55 (1.70-3.83)	1.77 (1.12-2.79)	0.014
Mechanical ventilation	1.58 (1.25-2.00)		
Pressure ulcer	1.45 (1.15-1.84)		
Fentanyl	3.74 (1.91-7.19)		
ECG/RASS			
ECG/TCE	0.78 (0.61-0.99)		
RASS	1		
Anticonvulsants	1.47 (1.17-1.86)	1.24 (1.00-1.55)	0.049
Muscle Relaxants	1.94 (1.45-2.59)	1.89 (1.43-2.48)	<0.001

*PR - Prevalence Ratio; †PRa - Adjusted Prevalence Ratio; CI95% - 95% Confidence Interval

Discussion

In our study, the mean age for *delirium* was 49.8 years, compared to 44 years for those without *de-*

lirium. Age is a critical risk factor for *delirium*. One study indicated that surgical or critical patients aged 72 to 86 years of age develop *delirium* during hospitalization.[17] Predisposition to *delirium* seems to increase with aging, as hospitalized older adults are more likely to develop confusional mental states.[18] However, both age groups in our sample were characterized by middle-aged individuals. This can be explained by the cause of hospitalization, mostly associated to trauma and neurovascular injuries.

Surgical patients were more likely to develop *delirium* in our sample; however, both surgical and clinical neurological patients were significantly at risk, particularly those with strokes and traumatic brain injury. Other studies investigated the relationship between cause of hospitalization and *delirium*. Mesa et al.[19] found a higher prevalence among clinical patients, while Wang et al.[20] found that neurosurgical ICU patients had had a higher incidence (42.2%) 4.5 days after admission. Wang also described that patients subjected craniotomies or other surgeries longer than 3 hours had higher prevalence of *delirium.*[20]

Our results reflect the local characteristics of Sergipe ICU were trauma and cerebral injury account for the majority of admissions. Intracranial hematomas (epidural or subdural), traumatic brain injury reduce frontal and temporal brain volume; therefore, mood and behavioral changes are expected among our subjects[21] and may explain the higher prevalence of *delirium* in our sample.

Additionaly, mechanic restraint, enteral nutrition, and mechanic ventilation were associated (*p<0.001)* with *delirium* in our study along with pressure ulcer (p=0.004), GCS/ TBI (p=0.041), fentanyl (p<0.001), noradreline *(*p=0.021), anticonvulsants (p=0.002) and muscle relaxant (p=0.027).

We found a significant correlation [RP 3,00 (2,08-4,22); p<0,001] between *delirium* and physical restraint, that is, when a patient is physically restrained to its hospital bed. Other studies corroborate to this evidence. Kwizera et al.[22] found that about 80% of physically restrained patients exhibit *delirium*. A lower *delirium* prevalence (39%) was observed in a case-control study with physically restraining Chinese ICU patients conducted by Pan et al.[4] A Swiss multicenter ICU study investigated the pros and cons of mechanic restrain exploring the controversial aspects and adverse events associated with this intervention. The authors evaluated the decision of its implementation in healthcare practice and found that physical restrain is effective in preventing adverse events.[23]

Conversely, Palacios-Ceña investigated physical restraint in Spanish ICUs with a focus group of physicians and nurses reporting indiscriminate use of restrictions.[24] Furthermore, *delirium* was underdiagnosed, undertreated, and confounded with other mental confusion pathologies. In the same study, physicians were not prompt to diagnose *delirium* and prescribed drug pharmacodynamics and pharmacokinetics uncarefully. This fact worsened during night shifts, and the choice of medication was determined without a clearly defined protocol.

Delirium was associated with enteral tube feeding in previous studies.[25-27] A study conducted at a university hospital in São Paulo, Brazil, indicated that 36.4% of patients with enteral nutrition had *delirium*. Conversely, *delirium* was an independent predictor for 20% tube feeding indications.[25] Individuals experiencing *delirium* are more likely to remove their enteral tube and suffer adverse events that may prolong their hospitalization and worsen clinical condition. A study conducted in a private ICU in Rio de Janeiro, Brazil, indicated that 50% of patients removed their tube feeding and this adverse event was associated with cognitive impairment, confusion, and *delirium.*[26] Association between patients removal of tube feeding and cognitive impairment is well-documented in the international literature, mainly observed in 79.3% of patients in a Chinese study.[27]

Mechanical ventilation was associated with *delirium*[27,28] and increased the duration of mechanical ventilation by 1.85 times.[28] A multicenter study between United States and Canada found that *delirium* patients had twice the duration of mechanical ventilation and hospitalization lengths 1.5 times longer than others without *delirium.*[28]

Jeon et al.[29] investigated the association between *delirium* and wean off from a mechanical ventilation. Results indicated that non-*delirium* pa-

tients were easily weaned out of mechanical ventilation, had fewer adverse events, and lower need for respiratory support.

Data summarized here may reflect the increased incidence *delirium* among mehanically ventilated patients. Consequently, when weaning off mechanical ventilation and removal of the endotracheal tube are successful, verbal communication can be restored, potentially promoting physical comfortable, and reducing pain. Besides, it can also reduce anxiety, agitation and impaired communication caused by the endotracheal tube. Thus, the incidence of *delirium* on mechanically ventilated patients should be investigated, aiming to guide the healthcare team decision-making based on the patient's clinical conditions, pain-management, and communication in ICU.

Sedation was another risk factor for *delirium* in our study. Hsieh and colleagues measured the impact of implementating of bundle protocol to awaken sedation, monitoring, and management of *delirium.*[30] This package decreased the days of restraint (30% to 26%; <0.001) and led to significant reductions in the length of mechanical ventilation and hospitalization, and reduced hospital costs. The authors also proposed a combination of reduction on daily sedation and passive movement, reducing the risk of pressure ulcers. The findings corroborate that early mobility, regardless of the use of mechanical ventilation, should be adopted whenever it is possible.

Thus, the vulnerability of patients on mechanical ventilation to *delirium* should be investigated. The non-use of artificial ventilation, when appropriate based on the patient's clinical conditions, favors communication and minimizes episodes of painful and unpleasant sensations that one may experience in ICU.

In this paper the *delirium* group, approximately 24.8% of the individuals were sedated with fentanyl. This finding is related to an increase s associated with an increase in the prevalence of *delirium* more than three times, while the use of anticonvulsants was almost twice as high.

Sedation is commonly used to support medical treatment of critically ill patients in the ICU. In this study, fentanyl, anticonvulsants, and norepinephrine were significantly associated with *delirium*. Fentanyl is a well-established sedative, used to reduce anxiety and stress[31] while phenytoin, is an anticonvulsant commonly linked to *delirium.*[32]

Aside from medication, our study found that pressure ulcers were prevalent, although not statistically significant [RP 1.45 (1.15-1.84)] among participants experiencing *delirium*. A Brazilian study[33] identified that over 80% of sedated patients experienced 28 adverse events, and pressure ulcer was the most prevalent of them. Taken together, the factors described above, including sedation, physical immobility, and restriction to a hospital bed can lead to diminished tissue oxygenation and increased the risk for pressure ulcers in patients with *delirium*.

Interestingly, we also observed that the use of muscle relaxants and anticonvulsants increased the prevalence of *delirium*. In our study, 37.9% of patients were diagnosed with severe or moderate Traumatic Brain Injury (TBI), which may increase upsurge convulsant episodes. Previous studies found that severe and moderate TBI elevate the incidence of convulsive episodes, particularly those patients with intraparenchymal hemorrhage.[34] Phenytoin was the drug of choice for anticonvulsant treatment and positively associated with *delirium* prevention. Another study highlighted the relationship between phenytoin and *delirium* suggesting an impact on the central nervous system causing nystagmus, ataxia, reduction in coordination and mental confusion, dyskinesia, dystonia, tremor, and others.[35]

Our study highlights the need for improvement through scientific evidence on the identification of *delirium* and its risk factors. Further studies are warranted to ascertain benefits, applicability, effectiveness, and costs in monitoring and treatment of *delirium*. Our study has limitations. It is an observational study and does not identify the source or causation for factors here associated with *delirium*. Second, subjects enrolled in this study were evaluated by multiple investigators due to the hospital characteristics, and schedule, which may imply bias or errors at assessment. Lastly, despite the large sample size, we collected data at one hospital only, which may limit the generalization of our data.

Conclusion

Our study indicated a 45.9% prevalence of *delirium* in adult participants (mean age 49.8 years old). Key associated factors with *delirium* include physical restraint, tube feeding for enteral nutrition and mechanical ventilation. Use of anticonvulsants and muscle relaxants were associated with *delirium* on multivariate analysis. Additionally, *delirium* patients exhibit more pressure ulcers, received more fentanyl, noradrenaline, and anticonvulsants. We highlight the importance of screening ICU *delirium* and its risk factors, investigating the many confounders that keep *delirium* neglected or underreported. The epidemiological description and associated factors identified in our study shed light on *delirium* occurrence from a regional perspective. Thus, the present study need more research that care planning for best clinical practices for sedation, respiratory e nutritional support, among with other risk factors *delirium* in intensive care unity.

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Colaborações

Pinheiro FGMS, Santos ES, Barreto IDC, Weiss C, Oliveira JC, Vaez AC e Silva FA contributed to the study design, data analysis and interpretation, article writing, relevant critical review of intellectual content and approval of the final version to be published.

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