Delirium Risk Factors in Hospitalized Patient: a Comprehensive Evaluation of Underlying Diseases and Medications in Different Wards of a Large Urban Hospital Center in Iran

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Abstract

Background: Delirium is a neurobehavioral syndrome, which is characterized by fluctuation of mental status, disorientation, confusion and inappropriate behavior and it is prevalent among hospitalized patients. Recognizing modifiable risk factors of delirium is the key point for improving our preventive strategies and restraining its devastating consequences. The present study investigated a wide range of possible predisposing factors of delirium, mainly focused on underlying diseases and mediations, of hospitalized patients in the different wards of a general hospital.

Method: In a prospective, observational trial, we investigated 220 patients who had been admitted to the internal, emergency, surgery and hematology-oncology departments. We employed the Confusion Assessment Method (CAM) questionnaire, The Richmond Agitation Sedation Scale (RASS), the General Practitioner Assessment of Cognition (GPCOG), demographic questionnaire, patient interviews and medical records. Multivariate logistic regression models were used to analyze predictive value of medications and underlying diseases for daily transition to delirium.; demographics were analyzed using univariate analysis to identify those independently associated with delirium.

Results: 220 patients were enrolled; the emergency department had the most incident delirium (%31.3) and the surgery section had the least (%2.4); delirium was significantly correlated with older ages and sleep disturbance. Among multiple underlying diseases and the medications evaluated in this study, we found that history of dementia, neurological diseases and malignancies increase the odds of transition to delirium and the use of anticoagulants decreases the incident delirium.

Conclusion: Approximately, 1 out of 10 overall patients developed delirium; Considering underlying diseases and the medications as the predisposing factors of delirium would help to better predict those at risk.

Introduction

Delirium is a neurobehavioral syndrome, which is characterized by fluctuation of mental status, disorientation, confusion and inappropriate behavior[3]. Disturbance of serum metabolites , neuroendocrine systems and neurotransmitters - specially cholinergic and dopaminergic systems- are assumed to play roles in delirium's pathophysiology by disrupting the neuronal activity[4-6]. The point prevalence of the delirium in patients over the age of 65 is more than 7.8%[7] and its incidence rate in hospitalized patients differs based on the underlying condition: it ranges from 5% to 87% [8, 9] -with overall higher incidences in intensive care unit (ICU) patients.

Well known risk factors of delirium consist of: cognitive impairment, dementia, hypertension, depression, history of stroke and older ages[10, 11]. Metabolic diseases such as hepatic encephalopathy, neuroendocrine disorders such as diabetes and certain classes of drugs like benzodiazepines, high dose narcotics, and anticholinergic medications have been linked to increased risk of delirium [12, 13] .Other known risk factors of delirium that by decreasing the perception of environment, increase the odds of

developing delirium consisted of: Inappropriate ambient light, sleep disorders and visual and hearing impairments.

Delirium increases the mortality rate, lengthen the hospitalization and places a heavy burden on hospitals and long-term care facilities[14]; delirium is also hard to diagnose and treat. So, to prevent delirium, its prevalence in each medical section and its associated risk factors should be characterized properly. The purpose of our study is to provide means for the early diagnosis and prevention of this syndrome among hospitalized patients by identifying the possible risk factors; so in a prospective, observational cohort study of 220 patients of several medical sections, we determined the incidence of delirium and evaluated its associated risk factors.

Methods

We enrolled patients from June 17, 2019 through September 2, 2019. All patients admitted to internal, surgical, emergency and hematology-oncology wards of Imam Khomeini hospital, Tehran, Iran were evaluated and 220 patients were included to the study. Enrollment criteria included: 1- all patients 18 years or older, 2- not requiring mechanical ventilation. Exclusion criteria were as follows: 1- symptoms of withdrawal or intoxication (Based on clinical evaluations and Paraclinical tests and interviews with patient companions) 2- moribund patients not expected to survive >24 hrs Decreased level of consciousness (RASS score -4 or -5, which considered as coma) [15, 16] 3- Inability to understand or speak Persian. Patients were followed up until they were discharged from the hospital or developed delirium.

As shown in figure 1, at first, baseline demographics as well as information pertaining to known risk factors for delirium were obtained through patient interviews and medical records. These included age, sex, city of residency, level of education, marital status, employment status, number of family members and the patient's general status information such as vision and hearing impairment and also access to visual and auditive aids if needed, quality and quantity of sleep, underlying diseases and medications.

Patients were evaluated once daily for delirium: at first, the level of consciousness was measured by The Richmond Agitation Sedation Scale (RASS) and if the RASS score was above -4 (-3 to +4) – the RASS score of -5 or -4 is considered as coma- then the confusion assessment method (CAM) questionnaire[1, 2] and the General Practitioner Assessment of Cognition (GPCOG) test was employed.

The Richmond Agitation Sedation Scale (RASS) is a valid instrument to measure the level of arousal; it is a 10-point scale ranging from -5 to +4: score of 0 represents a calm and alert state. Positive RASS scores indicate aggressive status and the negative RASS scores imply decreased levels of consciousness. The CAM questionnaire assesses the presence, severity, and fluctuation of 9 delirium features: acute onset, inattention, disorganized thinking, altered level of consciousness, disorientation, memory impairment, perceptual disturbances, psychomotor agitation or retardation, and altered sleep-wake cycle, and GPCOG test is used to evaluate patients for cognitive impairments and it is consisted of two components: a cognitive assessment and an informant questionnaire. The cognitive assessment includes nine items,

each correct answer is valid one point leading to a maximum score of 9; results =9 or <5 considered to be cognitively intact or impaired, respectively. Informant questionnaire only considered necessary if the cognitive test is equivocal (5-8 scores), the informant questionnaire query an informant (person who knows the patient well) six historical questions, a score of 0-3 indicates cognitive impairment and requires further investigations.

Statistical analysis

Chi square test was used to investigate the correlation between nominal and ordinal variables, after that the normality of variables was examined by Kolmogorov- Smirnov test; independent t-test was performed to investigate the relationship between numeric variables with normal distribution and delirium. Mann Whitney U statistical test was used to evaluate the difference between numeric variables with abnormal distribution. Adjusted odds ratios (OR) and confidence intervals (CI) were calculated for factors with significant univariate correlations.

Logistic regression was used to evaluate the predictive value of the significant risk factors, and the Hosmer and Lemeshow test was used to assess the fit of the risk prediction models; delirium was considered as dependent variable and the significant risk factors as independent variables(x) and the risk factors were compared one by one with the dependent variable (delirium). Regression coefficients with 95%-confidence intervals (CI) and the corresponding p-values were calculated for each risk factor. Moreover, odds ratios (OR) with 95%-CI were determined in the logistic regression.

Since, some patients had been concurrently afflicted by multiple diseases or been used multiple drugs, with regards to confounding effects of underlying diseases or drugs on each other, justified odds ratios were calculated. However, due to the low number of patients with hyperlipidemia and liver disorders, the adjusted odds ratios were not calculated in these two subgroups.

All data were analyzed using the 11th version of Stata and the first-order error(α) equal to 0.05 was considered to be statistically significant.

Results

Of the 220 patients studied, 114 were male (51.9%) and the average age was 59.3 years (SD= 13). Of these patients, 112 patients (50.9%) hospitalized in the internal ward, 83(37.7%) in the surgery section, 16(7.2%) in the emergency department and 9(4.09%) in hematology-oncology ward. The overall prevalence of delirium was 10%, and we obtained the highest prevalence in the emergency department (31.3%) and the least in the surgical section (2.4%). Patients developed delirium on average 4 days after hospitalization, that it was ranged from 1 to 14 days (median= 2, IQR= 3).

The overall prevalence of delirium in the study was 10%, which it differed in various sections of the hospital; we obtained the incidence of delirium as follows: emergency department 31.3%, hematology-oncology ward 22.2%, internal ward 11.6%, and surgery section 2.4% (Table 1).

Table 1. Prevalence of delirium by ward

Ward	affected	Not affected	Prevalence
Internal	13	99	11.6%
Surgery	2	81	2.4%
Emergency	5	11	31.3%
Hematology-Oncology	2	7	22.2%
Total	22	220	10%

By analyzing demographic indicators, we found significant association between age (p-value= 0.014) and the incidence of delirium, but there was no significant correlation between incidence of delirium and gender (p-value= 0.857), education (p-value= 0.414), city of residency (p-value= 0.386), employment status (p-value= 0.395), living with family members (p-value= 0.178) and marital status (p-value= 0.093).

By examining the clinical signs and using the information obtained from the interview, we found that the incidence of delirium was significantly associated with dementia (p-value= 0.008) and had a negative correlation with the quantity of sleep hours (p-value<0.0001) and its quality (p-value< 0.0001). However, there was no significant correlation between type of vision and hearing impairment (p-value= 0.336, 1.000 respectively), use and access to hearing aids (p-value=1.000, 1.000 respectively) and visual aids (p-value= 0.052, 0.274 respectively), sleep habits (p-value= 1.000), and visual and hearing health status (p-value= 0.056, 0.795 respectively)(Table 2).

Table 2. Demographics and delirium interview information of the patients

Factors	Delirium		P-value	Factors	Delirium		P-value
	Affected No. (%)	Not- affected No. (%)			Affected No. (%)	Not- affected No. (%)	
Vision				Sex			
Intact	3(13.64)	67(34)	0.056	Male	11 (50)	103 (52)	0.857
Impaired or blind	19(86.36)	130(66)		Female	11 (50)	95 (48)	
Type of visual loss				City of residence			
Partial	18(94.7)	128(98.5)	0.336	Capital	11 (50)	80 (40.4)	0.386
Total	1(5.3)	2(1.5)		Others	11 (50)	118 (59.6)	
Use of eyeglasses				Education			
Yes	6(33.3)	75(57.7)	0.052	Illiterate	11 (50)	75 (37.9)	0.414
No	13(66.7)	55(42.3)		Under diploma	9 (40.9)	81 (40.9)	
Access to eyeglasses				Diploma	0 (0)	21 (10.6)	
Yes	3(16.7)	41(31.5)	0.274	University degree	2 (9.1)	21 (10.6)	
No	15(83.3)	89(68.5)		Marital status			
Hearing				Married	13 (59.1)	152 (76.8)	0.093
Intact	17(77.3)	148(74.7)	0.795	Single	0 (0)	5 (2.5)	
Impaired or deaf	5(22.7)	50(25.3)		Widow	9 (40.9)	35 (17.7)	
Type of hearing loss				Divorced	0 (0)	6 (3)	
Partial	5(100)	47(94.2)	1.000	Employment status			
Total	0(0)	3(5.8)		Employed	3 (13.6)	37(18.7)	0.395
Use of hearing aid				Retired	2 (9.1)	38 (19.2)	

Yes	0(0)	5(9.8)	1.000	Unemployed	17 (77.3)	123 (62.1)	
No	5(100)	45(90.2)		Insurance			
Access to hearing aid				Yes	12 (54.6)	122 (61.6)	0.519
Yes	0(0)	3(5.9)	1.000	No	10 (45.4)	76 (38.4)	
No	5(100)	47(94.1)		Living with family members			
Dementia				Yes	19 (86.4)	186 (93.9)	0.178
Yes	3(13.6)	2(1)	0.008	No	3 (13.6)	12 (6.1)	
No	19(86.4)	196(99)		Age			
Comfortable sleep					65.7* (12.8**)	58.6(12.8**)	0.014
Yes	2(9.1)	122(61.6)	0.0001				
No	20(90.9)	76(38.4)					
Adequate sleep							
Yes	3(13.6)	171(86.3)	0.0001				
No	19(86.4)	27(13.6)					
Sleep habits							
Yes	1(4.5)	15(7.6)	1.000				
No	21(95.5)	183(92.4)					

*mean age of the group

**standard deviation

Since some patients had several diseases at the same time, adjusted statistical ratios were used to eliminate this confounding factor and based on that, we found significant association between delirium and underlying dementia, neurological diseases and malignancies. but, didn't find any significant correlation between delirium and diabetes, hypertension, hyperlipidemia, cardiovascular disease, renal, hepatic, Pulmonary and infectious diseases(Table 3).

Table 3. Analyzing the underlying diseases and medications of the patients for delirium

Underlying disease	adjusted		Drug group	adjusted	
	OR (CI)	P-value		OR (CI)	P-value
Dementia	10.6(1.2-93.9)	0.034	Anti-diabetics	0.5(0.1-2.3)	0.152
Diabetes	2.6(6.9-7.0)	0.072	Anti-hypertensives	0.7(0.1-3.7)	0.432
Hypertension	1.1(3.0-5.3)	0.843	Diuretics	0.4(0.1-1.3)	0.124
Hyperlipidemia	-	-	Antibiotics	2.3(0.5-9.8)	0.086
Cardiovascular disease	0.9(1.2-3.0)	0.874	Anti-hyperlipidemics	0.6(0.1-2.8)	0.361
Kidney disease	1.1(2.2-6.0)	0.951	Analgesics	1.4(0.3-5.6)	0.463
Liver disease	-	-	Anti-coagulants	0.3(0.0-1.9)	0.029
Neurologic disease	8.1(6.1-31.2)	0.002	Chemotherapy	0.2(0.1-3.2)	0.078
Malignancies	3.3(8.0-10.1)	0.048	Anti-convulsant	0.2(0.1-3.2)	0.078
Lung disease	1.4(7.2-12.0)	0.737	Sedatives	2.1(0.16-3.5)	0.481
Infectious disease	1.2(5.9-15.0)	0.899	Opioids	0.9	0.861

we found a significant correlation between anticoagulant use and delirium. No significant association was found between delirium and use of anti-diabetic, anti-hypertensives, diuretics, antibiotics, anti-hyperlipidemics, analgesics, chemotherapy agents, sedatives, opioids and anti-convulsants; nevertheless, antibiotics(p-value=0.086), chemotherapy agents(p-value=0.078) and anticonvulsants (p-value=0.078) had a near significant p-value and needed to be further investigated.

Discussion

Our study is a prospective, observational trial that evaluated the incidence rate of delirium and its contributing risk factors in 220 patients admitted to the internal, emergency, surgery and hematology-oncology departments.; first, we found that 1 out of 10 overall patients developed delirium; the emergency department had the most incident delirium (%31.3) and the surgery section had the least (%2.4). Second, by assessing the demographic indicators and general status information of included patients, we found a meaningful positive correlation between the incident delirium, and older ages and sleep disturbance; but we found no significant correlation between delirium and gender, employment status, sleep habits, living with family members, marital status, educational degree, visual or auditory impairment and access to visual and hearing aids. Third, by utilizing multivariate regression analysis for multiple underlying diseases and the medications, we found that history of dementia, neurological diseases and malignancies increase the odds of transition to delirium and the use of anticoagulants decrease the

incident delirium, but the correlation of delirium and other underlying diseases like diabetes, hypertension, cardiovascular disease, renal, Pulmonary and infectious diseases and also other medications wasn't meaningful.

The 10% incidence of delirium in this study is concordant with previous reports[17] and is lower than of the higher incidences reported by most of the other studies[17, 18]. This salient discrepancy might be originated in differences in patient characteristics (e. g., the average age, the severity of underlying condition, type of the diseases), the screening instrument and its application and assuming the Drug-induced sedation and medication-associated coma as delirium. And also the differences of delirium prevalence seen in our under study wards, could be due to differences in follow-up length, the patient characteristics and their specific medications [19]; the lower incidence of delirium in the surgical ward comparing to the internal ward, could be due to younger ages and also, most of them were at non-urgent surgery condition with a good health background.

The sleep hours and its quality, as reported by previous studies, have a strong correlation with delirium. The disturbed neurotransmission underlies this relationship: the REM cycles of the sleep adjust the acetyl choline and dopamine neurotransmission; and the both cholinergic and dopaminergic systems are reported to be dysregulated in the delirium state [20, 21]. Sleep habits, like the sleep time or afternoon naps, have not been associated with incident delirium. Baseline cognitive deficits were associated with an increased risk of developing delirium[4]; The presence of dementia and neurological disorders, through decreasing cerebral oxidative metabolism, cholinergic deficiency and inflammation increase the odds of developing delirium[22].

Malignancies are known to increase the chances of developing delirium through their adverse effects on the immune system, the blood-brain barrier, and the nervous system[23]. The number of patients with malignancy involved in this study was not enough to evaluate the specific subtypes of malignancies for delirium, but according to previous studies, the patients with primary or secondary CNS tumors, cancers with paraneoplastic neurological features and terminal cancers are at higher risks to develop delirium[24, 25]; however, taking the chemotherapy medications that were reported as predisposing factor for delirium in previous studies, were not associated with higher risks of delirium in our study. Because of insufficient number of the patients with hyperlipidemia and liver disease, we weren't able to analyze these two variables; according to previous studies, hyperlipidemia plays a protective role by strengthening the blood-brain barrier and liver diseases by disturbing plasma metabolites and electrolytes are risk factors for delirium[26-28].

In spite of other studies reported a relationship between delirium and diabetes[29], we couldn't find an association between them; diabetes mellitus is a chronic disease that is often accompanied by other diseases and also, the diabetic patients receive numerous medications; hence, to find out whether diabetes increase the odds of developing delirium, these all covariates should be evaluated cautiously. Siew et al.[30] reported that acute kidney injury increases the odds of developing delirium; but we only evaluated the chronic kidney diseases in this study and didn't find a meaningful relationship. Infectious

diseases like urinary tract infections were reported to increase the chance of delirium [31]; but infectious diseases weren't associated to delirium in our study that could be due to the lack categorization and also, younger ages of our participants. The lack of relationship between delirium and cardiac and pulmonary disorders, which we obtained, resembles previous studies[26].

Assessments of the role of medications in developing delirium by previous studies is limited and inconsistent[32, 33]. So, we investigated the role of a wide range of prescribed drugs for developing delirium. The use of anticoagulants (warfarin, heparin and enoxaparin) decreased the odds of developing delirium that resembles previous studies about warfarin[34]. However, we couldn't find any relationship between delirium and other drugs, but the level of significance of chemotherapy agents and antibiotics were marginal and both increased the odds of developing delirium.

Several limitations of this investigation warrant consideration: first, our sample size limited our ability to evaluate some underlying diseases like liver diseases and hyperlipidemia and also specific subtypes of diseases like malignancies or drugs like chemotherapy medications and antibiotics. Second, we did not consider any laboratory values in our study because the diagnostic laboratory values for delirium are still in advances[35-37]. Third, we evaluated delirium once daily; based on the fluctuating nature of delirium, it's possible that some cases have been missed; by assessing patient's cognitive status more frequently (every 4–8 hours), this bias would be removed, but this task is difficult to accomplish in a research setting due to resource and time constraints and also it is burdensome to patients. Fourth, we investigated numerous covariates that were deemed relevant a priori; so, other covariates that weren't measured might have affected our results. The strengths of this study lay in its diverse sample of medical patients with different types of conditions.

Conclusion

In summary, we investigated a wide range of medical and demographical factors to find the predisposing factors of delirium; this study documents the prevalence and risk factors of delirium in a prospective study of patients admitted in different sections of a referral hospital. The adverse outcomes of developing delirium are burdensome for healthcare system and is accompanied by decreased quality of life and increased mortality and morbidity of hospitalized patients. Therefore, recognizing the predisposing factors of delirium is the first step to prepare the healthcare systems to decrease the incidence and restrain the consequences. Future studies would need to explore that by which molecular and biological mechanisms, the known risk factors of delirium increase its occurrence and also, more interventional studies in this area are needed to strengthen our preventive and therapeutic strategies that at the moment, are not effective enough to prevent or cure delirium in most of the patients.

Declarations

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The current study was authorized by the ethical committee at Tehran University of Medical Sciences and followed the requirements of the 2013 edition of the Helsinki Declaration. All participants completed and signed a written informed consent form, and all personal information was considered confidential.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIALS

Researchers can obtain the datasets used in the current work from the Tehran University of Medical Sciences upon request. The data sharing policies in the Tehran University of Medical Sciences follow local regulations of our institution.

COMPETING INTERESTS

The authors of this article declare no competing interest regarding current research.

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AUTHOR'S CONTRIBUTIONS

M.A., S.M., and E.Z. all contributed to the article's concept and early design. The measurements and data collection were done by A.B, B.A. and H.G. The technique, data interpretation, and preliminary analysis were all done by F.R. and M.A. E.Z. and A.P. assisted in the control and planning of the project. N.S. and S.M. examined the data, completed the final analysis, authored the text, and created the figures. A.H, B.A., H.G., F. R., and N. S. contributed to the interpretation of the findings and helped with the article. All authors discussed the findings and provided feedback on the work before approving the final version for publication.

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Figures

Figure 1

The flow chart of the study