Point Prevalence of Delirium and Its Subtypes in the Patients Admitted with Acute Coronary Syndrome in Cardiac ICU and Its Impact on Mortality

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ABSTRACT

Objective: To measure the point prevalence of delirium in the patients admitted to the cardiac ICU with acute coronary syndromes, with particular attention to the most commonly noted delirium and the impact on ICU mortality and length of ICU stay.

Study Design: Prospective cohort study.

Place and Study Duration: National Institute of Cardiovascular Diseases, Karachi Pakistan, from Mar and Jul 2021.

Methodology: Consecutive adult patients with age >18 years admitted to the cardiac ICU after acute coronary syndromes were assessed for delirium using the confusion assessment method (CAM)-ICU tool and Richmond agitation sedation score (>-3). The types of delirium were also assessed.

Results: 201 patients were enrolled, half of patients with ST-elevation MI (51.2%) and shock (45.8%). Delirium was identified in 71 (35.3%) patients, 30 (42.2%) had hypoactive delirium and 41 (57.7%) had hyperactive delirium. In multivariable regression, independent risk factors for delirium were: sepsis 3.19 (1.15-8.87), uremia 4.12 (1.18-14.46), mechanical ventilation 7.58 (1.2-47.99), and non-invasive ventilation 8.55 (2.9-25.2). Overall mortality was 35 (17.4%); 27/71 (38%) vs. 8/130 (6.2%); *p* 0.001 in patients with and without delirium, respectively. In multivariable regression, delirium was an independent risk factor for mortality at 7.12 (2.16-2.23). The mean ICU stay was 7.772.36 days vs. 3.91.44 days; *p* 0.001 for patients with and without delirium.

Conclusion: The deleterious effect of delirium in terms of higher morbidity and mortality cannot be overemphasised. Hypoactive delirium is as common as the hyperactive type, with the same mortality risk. Assessment for delirium is mandatory for all patients admitted to the cardiac ICU.

Keywords: Acute coronary syndromes, CAM-ICU, Delirium, Mortality.

How to Cite This Article: *Taimoor L, Baloch K, Ikhlaq U, Abubaker J, Ansari I, Din NSU, Khan M. Point Prevalence of Delirium and Its Subtypes in the Patients Admitted with Acute Coronary Syndrome in Cardiac ICU and Its Impact on Mortality. Pak Armed Forces Med J 2022; 72(2): 408-413. DOI: https://doi.org/10.51253/pafmj.v72i2.7444*

INTRODUCTION

Delirium is a state of acute dysfunction of the central nervous system, characterised by varying levels of cognition and consciousness. Its spectrum ranges from coma and stupor at one end to normal awakening with the abnormal perception of the surrounding at the other.[1] Its frequency varies at approximately 37% in adult intensive care units (ICUs) patients 2 and 33.5% following cardiac surgery.[3] Inciting factors include older age, baseline cognitive impairment, metabolic derangements, abnormal blood glucose, sepsis, acidemia, drugs and tobacco withdrawal, and shock.[2] Additional risk factors in ICU are poor sleep hygiene, lights and alarms, intravenous and urinary catheters, immobilisation, tightly fitting masks for non-invasive ventilation and physical restraints.[4] delirium is classified into subtypes according to motor symptoms; hyperactive, hypoactive, and mixed. Patients with hyperactive delirium may show agitation, aggression and restlessness, while hypoactive may exhibit apathy, inattention, motor retardation and somnolence. The mixed type is characterised by rapid fluctuation between the hypoactive and hyperactive types observed over several hours. Rarely do patients show cognitive impairments without motor symp-toms.[5]

Delirium in the ICU portends a poor prognosis with more prolonged ICU and hospital stays and independent increases in mortality. The most validated screening tools for delirium detection are the confusion assessment method-ICU (CAM-ICU) and the intensive care delirium screening checklist (ICDSC). Other less commonly used scales are the memorial delirium assessment scale, delirium rating scale (DRS), and nursing delirium screening checklist.[6,7] ICDSC is assessed over a minimum of 8 hours, with reported 81.0% sensitivity and 87.7% specificity, and has limited application to intubated patients.[8] CAM-ICU, develo-ped by Ely and their team, relies on non-verbal tasks to detect delirium in patients admitted to the ICU. Delirium is diagnosed

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Received: 28 Sep 2021; revision received: 25 Jan 2022; accepted: 01 Feb 2022

when patients demonstrate acute and fluctuating changes in mental status with inattention measured by an auditory or visual test and either an altered level of consciousness or disorganised thinking with an intact level of consciousness. It can be applied to mechanically ventilated patients.[9] A comparison of CAM-ICU and IDSCI had a kappa coefficient of 0.80 (0.76–0.85) over seven days, indica-ting good agreement.[10] Objective assessment of consciousness, pertinent to delirium assessment, is done by RASS (Richmond agitation–sedation scale).

Delirium remains underdiagnosed with scarce information on the types and associations in patients after an acute coronary syndrome (ACS). Therefore, our study aimed to measure the point prevalence of delirium in ACS patients admitted to the cardiac ICU, focusing on the types of delirium and their impact on ICU mortality and length of ICU stay.

METHODOLOGY

This was a single-centre, prospective cohort study. We enrolled consecutive adult patients admitted after an ACS into the cardiac ICU of National Institute of Cardiovascular Diseases Karachi; a tertiary care referral hospital dedicated to cardiovascular diseases, from March to July 2021.

The sample size for the study was calculated with the expected frequency of delirium in the cardiac ICU as 15.3%.[11] At a 95% confidence level and 5% margin of error, the sample size of 201 was calculated using the WHO sample size calculator version 2.0.

Approval for the study was obtained from the Institutional Ethical Review Committee (ERC-27/2021). For participation in the study and publication, verbal informed consent was attained from patients or their representatives. The study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. No individual patient data was presented.

Inclusion Criteria: Patient of either gender, with age 18-98 years old, diagnosed with ACS (ST-elevation myocardial infarction-STEMI), non-STACS, including non-STEMI and unstable angina), intubated patients able to complete assessment, all the non-intubated patients, and patients with a RASS ≥ -3 were included in the study.

Exclusion Criteria: Patients with known cognitive disorders, RASS <-3, post-cardiac arrest patients with anoxic encephalopathy, and patients not expected to survive beyond 24 hours due to severe cardiogenic shock requiring high doses of vasopressors and refractory arrhythmias were excluded from the study.

Primary outcomes were the point prevalence, the subtype of delirium, and in-ICU mortality. Secondary outcomes were the length of ICU stay, the length of mechanical ventilation, and the non-mechanical ventilation required.

Patients were assessed within 24 hours of admission to the cardiac ICU. Patients not responding initially due to sedation were re-assessed once the sedation had worn off. Our ICU protocol for sedation included Opioids, Propofol, and Dexmedetomidine infusions. Benzodiazepines are used in unavoidable conditions such as delirium tremens or Benzodiazepine withdrawal syndromes. Baseline characteristics, type of ACS, and details regarding percutaneous coronary intervention (if done) were recorded.

Each patient's level of arousal was assessed using the bedside Richmond Agitation Sedation Scale (RASS). RASS is a 10-point scale ranging from -5 to +4, grading the level of alertness and agitation.[12] If the RASS score was higher than -3, the four steps of the CAM-ICU were applied. These consist of assessing (1) the acute onset of a fluctuating level of consciousness, (2) inattention, (3) disorganised thinking, and (4) altered level of consciousness. When non-verbal ratings and verbal ratings of CAM-ICU are compared, the non-verbal ratings have lower sensitivity (73%), a lower inter-rater reliability (0.64) and a higher specificity (100%).[13] Thus, we used a standardised format for verbal responses to questions such as "whether a stone would float on water?", "Are there fish in the sea?" and "is one kilo more than one pound?" All patients who could speak were instructed to address disorganised thinking and inattention with hand and head gestures for intubated or drowsy patients. A hypoactive type of delirium was consi-dered if the RASS score was 0 with consistent symptoms on the CAM-ICU, and a hyperactive type if the RASS score was 0 with consistent symptoms.

Once delirium was identified, the primary ICU services were notified, and modifiable risk factors were addressed, including pain control, removal of unnecessary invasive lines and catheters, daily sedation vacations, early mobilisation, and minimal use of sedation. Therapeutic interventions ranged from intravenous Haloperidol, Dexmedetomidine infusion, and atypical antipsychotics such as Quetiapine.

Statistical Package for Social Sciences (SPSS) version 21 was used for the data analysis. Continuous

data was tested for normality (with the help of the Shapiro-Wilk test); measures of central tendency were compared as mean and standard deviations (SD) using the t-test for normally distributed variables and as medians (interquartile range, IQR) using the Mann-Whitney U-test for skewed data. Categorical variables were compared using chi-square test or Fisher's exact test. For delirium and mortality, univariate and multi-variable logistic regression with backward variable selection was performed. The odds ratio (OR) with 95% confidence intervals (CI) was reported with the *p*-value of ≤0.05 was taken as statistically signi-ficant.

RESULTS

Two hundred one patients were enrolled in the study, out of which 120 (59.7%) were males and 81 (40.3%) were females. The mean age was 62.59 9.[16] All baseline characteristics were summarised in Table-I.

A total of 71 (35.5%) patients had delirium as per the CAM-ICU. 41/71 (57.7%) had hyperactive, and 30/71 (42.3%) had hypoactive delirium. Mortality in patients with delirium was 38% (27/71) vs. 6.2% (8/130) in patients without delirium, (*p* 0.001). There was no significant difference in mortality between the hypoactive and hyperactive types of delirium; 46.7% (14/71) vs. 31.7% (13/71) (*p*=0.200). Non-invasive mechanical ventilation, invasive mechanical ventilation, and the length of stay also got longer (Table-II), as did the number of days.

On multivariable logistic regression anxiolytics, uremia, sepsis, survival of cardiac arrest, non-invasive ventilation, and mechanical ventilation were independent risk factors for delirium (Table-III).

DISCUSSION

We found a point prevalence of 35.5% for delirium in patients with ACS admitted to a cardiac ICU, with increased ICU mortality, days on mechanical ventilation, and ICU duration. Hypoactive delirium occurred as commonly as the hyperactive type, with equally high mortality. The type of ACS did not affect delirium prevalence. Patients with ACS are at increased risk if they are older, are survivors of cardiac arrest, have concurrent sepsis, electrolyte imbalance, or require respiratory assistance.[14]

Our prevalence of delirium in the cardiac ICU was higher than in other studies. Naksuka *et al,* reported an incidence of 8.3% in the cardiac care unit.[15] This difference might be because Naksuka *et al*, included patients with both ACS and decompensated heart failure, whereas we included only patients after ACS, with the majority requiring revascularisation and aggressive management. Lahariya *et al,* reported an incidence of 28.8% in patients with a varied spectrum of cardiac conditions, some less severe than ACS.

Table-I: Baseline risk factors and characteristics according to type of acute coronary syndrome and prevalence of delirium, its subtypes and mortality.

Characteristics	n (%)
Gender	
Male	120 (59.7%)
Female	81 (40.3%)
Age (years) (mean ± SD)	**62.59 ± 9.16**
< 75 years	179 (89.1%)
≥ 75 years	22 (10.9%)
Acute Coronary Syndrome	
ST Elevation Myocardial Infarction	97 (48.3%)
Non-St Elevation Acute Coronary Syndrome	104 (51.7%)
Co-morbid Conditions	
Diabetes Mellitus	109 (54.2%)
Chronic Kidney Disease	34 (16.9%)
Chronic Heart Failure	145 (72.1%)
Hypertension	108 (53.7%)
Chronic Liver Disease	7 (3.5%)
Chronic Respiratory Failure	38 (18.9%)
Smoking	76 (37.8%)
Alcohol	7 (3.5%)
Anxiolytics	23 (11.4%)
Sodium Abnormality	45 (22.4%)
Uremia	69 (34.3%)
Glycemic Abnormality	95 (47.3%)
Sepsis	47 (23.4%)
Sedation in Last 24 Hours	52 (25.9%)
Vasopressor Use	92 (45.8%)
Survivors of Cardiac Arrest	34 (16.9%)
Arrhythmias	31 (15.4%)
IABP	21 (10.4%)
Noninvasive Ventilation	80 (39.8%)
Mechanical Ventilation	68 (33.8%)
Angioplasty	168 (83.6%)
RASS Score	
RASS ≥0	168 (83.6%)
RASS <0	33 (16.4%)
Delirium	
Yes	71 (35.3%)
No	130 (64.7%)
Type of Delirium	
Hyperactive	41/71 (57.7%)
Hypoactive	30/71 (42.3%)
Length of ICU stay (days)	5.27 ± 2.6
Duration of NIV used (days)	1.62 ± 2.14
Duration of MV (days)	1.32 ± 2.11
Mortality in Hospital	35 (17.4%)

IABP =intra-aortic balloon pump, ICU=intensive care unit, NIV=non-invasive ventilator, MV=mechanical ventilator, RASS=Richmond Agitation Sedation Scale

Table-II: Risk factor and difference in mortality, length of ICU stay and length of Respiratory support among patients who developed delirium vs. patients who did not develop delirium.

Characteristics	Delirium		*p*-value
	Yes, n=71	No, n=130	
Gender			
Male	41 (57.7%)	79 (60.8%)	0.676
Female	30 (42.3%)	51 (39.2%)	
Age (years)	66.08 ± 9.42	60.68 ± 8.46	<0.001*
<75 years	56 (78.9%)	123 (94.6%)	<0.001*
≥75 years	15 (21.1%)	7 (5.4%)	
Type of Acute Coronary Syndrome			
NST-ACS	28 (39.4%)	69 (53.1%)	0.064
STEMI	43 (60.6%)	61 (46.9%)	
Co-Morbid Conditions			
Diabetes Mellitus	48 (67.6%)	61 (46.9%)	0.005*
Chronic Kidney Disease	20 (28.2%)	14 (10.8%)	0.002*
Chronic Heart Failure	58 (81.7%)	87 (66.9%)	0.026*
Hypertension	41 (57.7%)	67 (51.5%)	0.399
Chronic Liver Disease	3 (4.2%)	4 (3.1%)	0.671
Chronic respiratory failure	20 (28.2%)	18 (13.8%)	0.013*
Smoking	33 (46.5%)	43 (33.1%)	0.061
Alcohol	5 (7%)	2 (1.5%)	0.042*
Anxiolytics	20 (28.2%)	3 (2.3%)	<0.001*
Sodium Abnormality	28 (39.4%)	17 (13.1%)	<0.001*
Uremia	43 (60.6%)	26 (20%)	<0.001*
Glycemic Abnormality	45 (63.4%)	50 (38.5%)	<0.001*
Sepsis	31 (43.7%)	16 (12.3%)	<0.001*
Sedation in Last 24 Hrs	39 (54.9%)	13 (10%)	<0.001*
Shock	52 (73.2%)	40 (30.8%)	<0.001*
Survivors of Cardiac Arrest	30 (42.3%)	4 (3.1%)	<0.001*
Arrhythmias	15 (21.1%)	16 (12.3%)	0.098
IABP	19 (26.8%)	2 (1.5%)	<0.001*
Noninvasive Ventilation	44 (62.0%)	36 (27.7%)	<0.001*
Mechanical Ventilation	52 (73.2%)	16 (12.3%)	<0.001*
Angioplasty	58 (81.7%)	110 (84.6%)	0.593
RASS Score			
RASS≥0	41 (57.7%)	127 (97.7%)	<0.001*
RASS<0	30 (42.3%)	3 (2.3%)	
Length of ICU Stay in Days	7.77 ± 2.37	3.9 ± 1.45	<0.001*
Duration of NIV used in Days	3.34 ± 2.32	0.68 ± 1.29	<0.001*
Duration of MV in Days	3.31 ± 2.36	0.24 ± 0.73	<0.001*
Mortality in Hospital	27 (38%)	8 (6.2%)	<0.001*

*STEMI=ST elevation myocardial infarction, NSTE-ACS= non-ST elevation acute coronary syndrome, IABP =intra-aortic balloon pump, ICU=intensive care unit, NIV=non-invasive ventilator, V=mechanical ventilator, RASS=Richmond Agitation Sedation Scale, *statistically significant at 5%*

Various risk factors were assessed, but the patient requiring respiratory assist devices was not documented in detail.[16] Hence, their incidence is lower but still comparable to our study.

Our study showed patients with delirium to have a more extended ICU stay and a longer duration of mechanical ventilation, which is comparable to what is reported in a cardiac surgery ICU at a hospital in Pakistan. They also showed hyperglycemia as an independent risk factor for delirium, which was not significant in our study on multivariate analysis.[17]

Our study showed hypoactive delirium to be as common as the hyperactive type. This contrasts with Delirium Cordis, which reported hypoactive delirium more commonly than the hyperactive type (42.9% vs. 12.5% p=0.02). A mixed type of delirium was also assessed in that study.[11] Our study did not assess the mixed subtype of delirium as its detection required several hours. This may have influenced mortality rates between the different subtypes of delirium. While exploring modifiable risk factors in a cardiac ICU, including medical and post-surgical patients, McPherson *et al,* reported the prevalence of the hypoactive sub-type of delirium to be 92%, which is considerably higher than our results. McPherson *et al,* used Benzodiazepines very frequently and Dexmedetomidine for routine sedation in ICU 18, which may cause the higher prevalence. Benzodiazepines are well known as risk factors for delirium.[19] The scarce use of Benzodiazepines in our ICU made hypoactive delirium less prevalent in our study.

Delirium is an easily treatable condition, albeit challenging to diagnose unless applied with special tools. This study emphasises the presence of delirium in patients after an acute coronary syndrome in the cardiac ICU. Continuous delirium screening and prevention efforts can reduce the perilous effects of delirium and overall morbidity and mortality. Mini-mising risk factors and following the validated ABCDEF bundle for delirium prevention is warranted in all the patients admitted to the Critical Care Unit.[20]

Our study had various strengths. We conducted this study in a cardiac ICU with patients post-ACS clarified modifiable and non-modifiable risk factors in this specific patient population. Before applying the CAM-ICU tool, translators were present for patients with different languages. Special attention was given to identifying the subtype of delirium.

Due to the nature of the presentation, hypoactive delirium can be easily missed during a routine assessment of patients. With its incidence as high as the hyperactive type with the same mortality risk,

Table-III: Uni-variate and multivariable logistic regression analysis for delirium risk factors.

Parameters	Uni-Variate		Multivariable	
	OR [95% CI]	*p*-value	OR [95% CI]	*p*-value
Male	0.88 [0.49 -1.59]	0.676	-	-
Age≥ 75 years	4.71 [1.82 -12.18]	0.001*	1.21 [0.24 -6]	0.816
STEMI	1.74 [0.97 -3.13]	0.065	-	-
Diabetes Mellitus	2.36 [1.29 -4.32]	0.005*	0.64 [0.17 -2.38]	0.502
Chronic Kidney Disease	3.25 [1.52 -6.94]	0.002*	1.48 [0.37 -6]	0.582
Chronic Heart Failure	2.21 [1.09 -4.46]	0.028*	3.23 [0.95 -11.03]	0.061
Hypertension	1.29 [0.72 -2.3]	0.399	-	-
Chronic Liver Disease	1.39 [0.3 -6.39]	0.672	-	-
Chronic Respiratory Failure	2.44 [1.19 -5]	0.015*	0.63 [0.15 -2.67]	0.529
Smoking	1.76 [0.97 -3.18]	0.062	-	-
Alcohol	4.85 [0.92 -25.67]	0.063	-	-
Anxiolytics	16.6 [4.73 -58.31]	<0.001*	10.97 [1.85 -64.98]	0.008*
Sodium Abnormality	4.33 [2.15 -8.69]	<0.001*	1.82 [0.47 -7.09]	0.385
Uremia	6.14 [3.23 -11.66]	<0.001*	4.12 [1.18 -14.46]	0.027*
Hypo/Hyperglycemia	2.77 [1.52 -5.04]	<0.001*	2.31 [0.66 -8.11]	0.192
Sepsis	5.52 [2.73 -11.15]	<0.001*	3.19 [1.15 -8.87]	0.026*
Sedation in Last 24 Hours	10.97 [5.24 -22.98]	<0.001*	0.43 [0.06 -3.24]	0.416
Shock	6.16 [3.23 -11.73]	<0.001*	0.97 [0.28 -3.33]	0.962
Survivor of Cardiac Arrest	23.05 [7.66 -69.32]	<0.001*	5.93 [1.04 -34.02]	0.046*
Arrhythmias	1.91 [0.88 -4.14]	0.102	-	-
Intra-Aortic Balloon Pump	23.38 [5.26 -103.99]	<0.001*	6.34 [0.92 -43.73]	0.061
Non-Invasive Ventilation	4.26 [2.3 -7.86]	<0.001*	8.55 [2.9 -25.2]	<0.001*
Mechanical Ventilation	19.5 [9.29 -40.93]	<0.001*	7.58 [1.2 -47.99]	0.032*
Angioplasty	0.81 [0.38 -1.75]	0.593	-	-

*OR=odds ratio, CI=confidence interval, STEMI=ST elevation myocardial infarction, *statistically significant at 5%, On multivariable logistic regression, delirium was confirmed to be an independent risk factor for mortality OR 5.16[95% CI: 1.47-18.17; p=0.011]*

Table-IV: Univariate and multivariable logistic regression analysis for mortality.

Parameters	Univariate		Multivariable	
	OR [95% CI]	*p*-value	OR [95% CI]	*p*-value
Male	1.17 [0.55-2.49]	0.676	-	-
Age≥ 75 years	2.52 [0.94-6.73]	0.066	1.07 [0.33-3.46]	0.913
STEMI	1.13 [0.54-2.35]	0.740	-	-
Diabetes Mellitus	1.54 [0.73-3.25]	0.262	-	-
Chronic Kidney Disease	1.6 [0.65-3.9]	0.305	-	-
Chronic Heart Failure	1.68 [0.69-4.09]	0.257	-	-
Hypertension	1.36 [0.65-2.86]	0.414	-	-
Chronic Liver Disease	0.78 [0.09-6.73]	0.825	-	-
Chronic Respiratory Failure	1.34 [0.56-3.25]	0.512	-	-
Smoking	1.49 [0.71-3.11]	0.290	-	-
Alcohol	0.78 [0.09-6.73]	0.825	-	-
Anxiolytics	1.81 [0.66-4.99]	0.249	-	-
Sodium Abnormality	3.98 [1.83-8.65]	<0.001*	2.22 [0.76-6.47]	0.144
Uremia	3.18 [1.51-6.73]	0.002*	1.15 [0.38-3.43]	0.807
Hypo/Hyperglycemia	1.62 [0.78-3.38]	0.200	-	-
Sepsis	3.14 [1.45-6.8]	0.004*	1.61 [0.64-4.03]	0.307
Sedation in Last 24 Hours	2.61 [1.22-5.61]	0.014*	0.61 [0.16-2.38]	0.477
Shock	3.14 [1.44-6.84]	0.004*	2.62 [0.81-8.52]	0.109
Survival of Cardiac Arrest	3.42 [1.49-7.83]	0.004*	1.03 [0.31-3.44]	0.956
Arrhythmias	0.9 [0.32-2.53]	0.838	-	-
Intra-Aortic Balloon Pump	2.08 [0.75-5.82]	0.161	-	-
Non-Invasive Ventilation	2.36 [1.12-4.94]	0.023*	1 [0.39-2.55]	0.996
Mechanical Ventilation	3.28 [1.55-6.93]	0.002*	0.66 [0.13-3.43]	0.620
Angioplasty	0.94 [0.36-2.48]	0.899	-	-
RASS<0	6.17 [2.69-14.13]	<0.001*	2.57 [0.92-7.2]	0.072
Delirium	9.36 [3.96-22.14]	<0.001*	4.86 [1.37-17.28]	0.015

*OR=odds ratio, CI=confidence interval, STEMI=ST elevation myocardial infarction, RASS=Richmond Agitation Sedation Scale, *statistically significant at 5%*

validated assessment for delirium is mandatory for all patients being admitted to the Critical Care Unit for early identification and treatment so that death, disability, and long-term cognitive impairment are avoided.

STUDY LIMITATIONS

Limitations included informal assessment of pain without applying a scoring system before assessing delirium; inability to identify the mixed subtype of delirium because the assessment was only done once every 24 hours; and glycemic and sodium abnormalities were not clearly defined as increased or decreased from the normal reference range.

ACKNOWLEDGEMENT

We thank Arsalan Younus, Abdul Hameed, and Syed Wahaj Azim for their assistance in data collection.

CONCLUSION

The deleterious effect of delirium in terms of higher morbidity and mortality cannot be overemphasised. Hypoactive delirium is as common as the hyperactive type, with the same mortality risk. Assessment for delirium is mandatory for all patients admitted to the cardiac ICU.

Conflict of Interest: None.

Authors' Contribution

LT: Conception, design, drafting, KB:, JA:, NSUD: Conception, design, review, UI: Design, drafting, data acquisition, IA: Interpretation, data acquisition, MK: Analysis and interpretation.

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