Incidence and risk factors of delirium in surgical intensive care unit

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Incidence and risk factors of delirium in surgical intensive care unit

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ABSTRACT

Background To evaluate the incidence and modifiable risk factors of delirium in surgical intensive care unit (SICU) of tertiary care hospital in a low-income and middle-income country.

Methods We conducted a single cohort observational study in patients over 18 years of age who were admitted to the SICU for >24 hours in Aga Khan University Hospital from January to December 2016. Patients who had pre-existing cognitive dysfunction were excluded. Intensive Care Delirium Screening Checklist was used to assess delirium. Incidence of delirium was computed, and univariate and multivariable analyses were performed to observe the relationship between outcome and associated factors.

Results The average patient age was 43.29±17.38 and body mass index was 26.25±3.57 kg/m². Delirium was observed in 19 of 87 patients with an incidence rate of 21.8%. Multivariable analysis showed chronic obstructive pulmonary disease, pain score >4 and hyponatremia were strong predictors of delirium. Midazolam (adjusted OR (aOR)=7.37; 95% CI 2.04 to 26.61) and propofol exposure (aOR=7.02; 95% CI 1.92 to 25.76) were the strongest independent predictors of delirium while analgesic exposures were not statistically significant to predict delirium in multivariable analysis.

Conclusion Delirium is a significant risk factor of poor outcome in SICU. There was an independent association between pain, sedation, COPD, hyponatremia and fever in developing delirium.

Level of evidence IV.

INTRODUCTION

Delirium in critically ill patients is common and distressing.1 The incidence of delirium in intensive care unit (ICU) ranges from 45% to 87%.2 3 Despite its high incidence in literature, the data are scarce in the low-income and middle-income world, especially in surgical patients. One of the reasons may be less sensitization and training of ICU staff, which can delay in prompt diagnosis and management.4 It is mostly labeled as dementia, depression or ICU syndrome in literature.5

Arguably, delirium is a well-recognized cause of morbidity and mortality among ICU patients. It causes longer hospital stay, lower 6-month survival and cognitive impairment persisting even years after discharge.6 Therefore, it is recommended that all ICU patients are assessed for delirium using a validated tool, which is not very common in most ICUs.7 In a study, published in 2008, the risk was observed 73% in surgical and trauma patients.8

The cause of delirium is almost always multifactorial, dependent on certain predisposing and precipitating factors. Some of the predisposing factors are not modifiable, for example, age, gender, addiction, pre-existing cognitive impairment, pre-existing cardiac and pulmonary disease. Modifiable factors can be environmental and acute illness such as no visible daylight, no clock, no visits, sedation, increase in length of stay, fever, pain, tubes and catheters. It is important to find out the risk factors associated with our patients and introduce guidelines to minimize the modifiable factors therefore preventing delirium in ICU. Moreover, the data and incidence of delirium are scarce in surgical cohort.

The purpose of this study was to evaluate the incidence and associated risk factors of delirium in surgical ICU (SICU) of tertiary care hospital.

METHODS

A single cohort prospective observational study was conducted in SICU of a teaching hospital. Our inclusion criteria included all those patients aged >18 years and had an ICU stay of >24 hours. Patients, who expired within 24 hours of admission, history of cognitive impairment, on any type of antipsychotic medications or patients with do not resuscitate status were excluded from the study because of the difficulty to assess delirium in this group. Patient’s eligibility in this study was evaluated by one of the trained investigators. A predesigned proforma was filled. The proforma included age, gender, comorbid conditions like cardiac, respiratory and renal impairment (hypertension, ischemic heart disease (IHD), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), reason of ICU admission, acute physiology and chronic health evaluation II (APACHE II) score, Glasgow Coma Scale and daily use of sedatives, opioids, steroids or antipsychotics drugs. The sedation level was assessed by using Riker Sedation-Agitation Scale (SAS). Patients were daily evaluated until their SAS score was ≥4, so they could be assessed for delirium using the 8-item Intensive Care Delirium Screening Checklist (ICDSC) every 8 hours until day 5 of ICU admission. Patient with an ICDSC score of 4 or higher was considered delirious. Analysis of whole blood count, arterial blood gases, biochemistry, culture and radiological examinations, such as chest X-ray, were performed as routine ICU measure as per physician discretion. We followed all clinical, laboratory findings and disease status, for instance, hypertension, respiratory diseases and DM as...
Patients admitted in SICU during study period (n = 200)

Assessed for eligibility (n = 200)

Excluded after screening (n = 113)
- Age < 18 (n = 13)
- Cognitive impairment (n = 47)
- ICU admission < 24 hours (n = 12)
- DNR patients (n = 26)
- Patients expired within 24 hours of ICU stay (n = 15)

After screening included Patients (n = 87)

With Delirium (n = 19)

Without Delirium (n = 68)

Figure 1 Flow diagram of patient in the study. DNR, do not resuscitate; ICU, intensive care unit; SICU, surgical intensive care unit.

Potential risk factor for delirium. Patients were followed until hospital discharge.

**Statistical analysis**

All statistical analyses were performed with the software SPSS V.19 (SPSS, Chicago, Illinois, USA). Incidence of delirium was computed by ICDSC and it was outcome variable. Age, body mass index (BMI), APACHE, hospital stay and ICU stay were estimated as mean±SD or median (25th−75th percentile) and analyzed by independent sample t-test or Mann−whiny U test between patients with and without delirium. Frequency and percentages were computed for all categorical variables and analyzed by χ² test or Fisher’s exact test. P values ≤ 0.05 were considered as statistically significant. In univariate analysis, those variables which had p value ≤ 0.20 were included in multivariable analysis. Multivariable logistic regression with forwarding stepwise method was used to observe the factors associated with delirium. The goodness of fit of the models was examined by Hosmer-Lemeshow goodness-of-fit tests.

**RESULTS**

From January to December 2016, we screened prospectively 200 patients who were admitted to SICU. A total of 87 patients were included who followed the inclusion criteria (figure 1). The average age of the patient was 43.29±17.38 years. There were 62 (78.2%) male and 19 (21.8%) female patients. Comorbidities were observed in 57.7% (50/87) cases and a total of 26 patients had more than one comorbidity. Hypertension was found in 30 (34.5%), DM 17 (19.5%), COPD 13 (14.9%), IHD 7 (8%) and 19 (31.3%) had other comorbidities. Neurosurgical and general surgery procedure were commonly performed as presented in table 1.

Delirium was assessed in five consecutive days in three time points on each day, there were 9.2% (8/87) patients who had delirium on day 1, 8.6% (6/79) on day 2, 2.7% (2/73) on day 3, 1.4% (1/71) on day 4 and 2.9% (2/70) on day 5. Cumulative incidence of delirium was observed in 21.8% (19/87) during the ICU stay. The onset of delirium commonly occurring on second day was 73.6% (14/19). In univariate analysis, COPD, fever, pain score > 4 on visual analog scale, agitation, sedation, hypernatremia (Na > 145), length of ICU stay ≥ 7 days and mortality were significantly high in those patients who developed delirium (table 2).

Midazolam and propofol were 4 times more likely to develop delirium as well as analgesic medication pethidine was also more likely to develop delirium in univariate analysis (table 3). The stepwise multivariable logistic regression showed that increasing OR of COPD, inadequate pain relief (pain score > 4) and hypernatremia were strong predictors of delirium (table 4) and in another model regarding the medication of sedation, midazolam (adjusted OR (aOR)=7.37; 95% CI 2.04 to 26.61) and propofol exposure (aOR=7.02; 95% CI 1.92 to 25.76) were the strongest independent predictors of delirium. Analgesic medications were not significant to predict delirium in multivariable analysis (table 5).

**DISCUSSION**

The overall incidence of delirium in our study is 21.8% in SICU, which is in the range, reported in the literature.6 However, higher incidence was found in many other studies which is explained by differences in definitions of delirium, ICU population (medical or surgical), the severity of illness and the diagnostic tool used.7 8 It is observed in our study that inadequate

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**Table 1** Characteristics of the patients according to incidence of delirium

| Variables         | Delirium (n=19) | Non-delirium (n=68) |
|-------------------|-----------------|---------------------|
| Age (years)       | 41.47±18.84     | 43.79±17.07         |
| Weight (kg)       | 72.63±12.28     | 72.68±11.77         |
| Height (cm)       | 167.16±8.17     | 165.88±6.54         |
| BMI (kg/m²)       | 25.91±3.36      | 26.36±3.63          |
| Gender            |                 |                     |
| Male              | 14 (73.7%)      | 54 (79.4%)          |
| Female            | 5 (26.3%)       | 14 (20.6%)          |
| Comorbid          | 14 (73.7%)      | 36 (52.9%)          |
| Hypertension      | 4 (21.1%)       | 26 (38.2%)          |
| Diabetic mellitus | 3 (15.8%)       | 14 (20.6%)          |
| IHD               | 3 (15.8%)       | 4 (5.9%)            |
| COPD              | 10 (52.6%)      | 3 (4.4%)            |
| Others            | 3 (15.8%)       | 16 (23.5%)          |
| Surgical procedure|                 |                     |
| Neurosurgical     | 5 (17.2%)       | 24 (38.2%)          |
| Gynecological     | 0 (0%)          | 4 (100%)            |
| General           | 13 (28.3%)      | 33 (71.7%)          |
| Others            | 1 (12.5%)       | 7 (18.5%)           |
| APACHE II*        | 18 (15−22)      | 18 (16−20)          |
| Length of ICU stay (days)* | 8 (5−12) | 5 (3−8) |
| Length of hospital stay (days)* | 21 (11−26) | 13 (8−21) |

Data are presented as n (%), means±SD.

*Median (25th−75th percentile). APACHE II, acute physiology and chronic health evaluation II; BMI, body mass index; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IHD, ischemic heart disease.
Table 2  Factors associated with delirium in univariate analysis

| Variables                      | N=87 | With delirium (n=19) | Without delirium (n=68) | OR (95% CI) | P value  |
|--------------------------------|------|-----------------------|-------------------------|-------------|----------|
| Age (years)                    |      |                       |                         |             |          |
| ≤40                            | 42   | 12 (28.6%)            | 30 (71.4%)              | 2.17 (0.76 to 6.19) | 0.142    |
| >40                            | 45   | 7 (15.6%)             | 38 (84.4%)              | Ref         | 0.593    |
| Gender                         |      |                       |                         |             |          |
| Male                           | 68   | 5 (26.3%)             | 54 (79.4%)              | 0.726 (0.22 to 2.36) | 0.726    |
| Female                         | 19   | 14 (73.7%)            | Ref                     |             |          |
| BMI (kg/m²)                    |      |                       |                         |             |          |
| ≥25                            | 47   | 9 (19.1%)             | 38 (80.9%)              | 0.71 (0.26 to 1.97) | 0.51     |
| <25                            | 40   | 10 (25%)              | 30 (75%)                | Ref         |          |
| COPD                           |      |                       |                         |             |          |
| Yes                            | 13   | 10 (76.9%)            | 3 (23.1%)               | 24.07 (5.55 to 104.33) | 0.0005*  |
| No                             | 74   | 9 (12.2%)             | 65 (87.8%)              | Ref         |          |
| Intubation                      |      |                       |                         |             |          |
| Yes                            | 78   | 18 (23.1%)            | 60 (76.9%)              | 2.4 (0.28 to 20.49) | 0.677    |
| No                             | 9    | 1 (11.1%)             | 8 (88.9%)               | Ref         |          |
| Fever                          |      |                       |                         |             |          |
| Yes                            | 25   | 10 (40%)              | 15 (60%)                | 3.92 (1.35 to 11.42) | 0.009*   |
| No                             | 62   | 9 (14.5%)             | 53 (85.5%)              | Ref         |          |
| Infection                      |      |                       |                         |             |          |
| Yes                            | 25   | 5 (20%)               | 20 (80%)                | Ref         |          |
| No                             | 62   | 14 (22.6%)            | 48 (77.4%)              |             |          |
| Pain ≥4                        |      |                       |                         |             |          |
| Yes                            | 19   | 11 (57.9%)            | 8 (42.1%)               | 10.31 (3.19 to 33.29) | 0.0005*  |
| No                             | 68   | 8 (11.8%)             | 60 (88.2%)              | Ref         |          |
| Agitation                      |      |                       |                         |             |          |
| Yes                            | 40   | 17 (42.5%)            | 23 (57.5%)              | 16.63 (3.53 to 78.26) | 0.0005*  |
| No                             | 47   | 2 (4.3%)              | 45 (95.7%)              | Ref         |          |
| Sedation                       |      |                       |                         |             |          |
| Yes                            | 54   | 16 (29.6%)            | 38 (70.4%)              | 4.21 (1.12 to 15.80) | 0.024*   |
| No                             | 33   | 3 (9.1%)              | 30 (90.9%)              | Ref         |          |
| Hypernatremia (serum sodium ≥145) |      |                       |                         |             |          |
| Yes                            | 42   | 16 (38.1%)            | 26 (61.9%)              | 8.61 (2.28 to 32.46) | 0.0005*  |
| No                             | 45   | 3 (6.7%)              | 42 (93.3%)              | Ref         |          |
| Serum creatinine ≥1.2          |      |                       |                         |             |          |
| Yes                            | 45   | 7 (15.6%)             | 38 (84.4%)              | 0.46 (0.16 to 1.31) | 0.142    |
| No                             | 42   | 12 (28.6%)            | 30 (71.4%)              | Ref         |          |
| Length of ICU stay (days)      |      |                       |                         |             |          |
| <7 days                        | 56   | 8 (14.3%)             | 48 (85.7%)              | Ref         | 0.022*   |
| ≥7 days                        | 31   | 11 (35.5%)            | 20 (64.5%)              | 3.3 (1.16 to 9.43) | 0.291    |
| Length of hospital stay        |      |                       |                         |             |          |
| ≤10                            | 32   | 4 (12.5%)             | 28 (87.5%)              | Ref         |          |
| 11–30                          | 44   | 12 (27.3%)            | 32 (72.7%)              | 2.63 (0.76 to 9.07) | 0.062    |
| >30                            | 11   | 3 (27.3%)             | 8 (72.7%)               | 2.63 (0.48 to 14.23) | 0.291    |
| Mortality                      |      |                       |                         |             |          |
| Yes                            | 21   | 11 (52.4%)            | 10 (47.6%)              | 7.97 (2.57 to 24.72) | 0.0005*  |
| No                             | 66   | 8 (12.1%)             | 58 (87.9%)              | Ref         |          |

* p value<0.05
*p value <0.05
BMI, body mass index; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit.

The relationship between opioid analgesics and delirium in critical care patients appear complex especially when examining the literature, given the seemingly conflicting results of observational studies. In ICU population, where opioids are used most often to treat pain (eg, in trauma and burn ICU populations), treatment with opioid analgesics has been associated with a...
reduced risk of delirium. Conversely, in general medical and SICU populations, where opioids are frequently used for sedation (either alone or in conjunction with other sedating medications, particularly benzodiazepines), treatment with opioid analgesics has been associated with an increased risk of delirium, particularly when their use induces a coma. However, there is significant reduction in delirium with good pain control.

Apart from acute illness, delirium can be precipitated by administration of certain medications. These are antihistamines, analgesics (particularly benzodiazepines), treatment with opioid analgesics, which is itself a risk factor for delirium associated with corticosteroids, which is itself a risk factor for delirium but in this study, steroid association with delirium could not be ascertainment. Most of the patients were prescribed intravenous hydrocortisone for the treatment of septic shock.

The presence of electrolyte disorders or an abnormal electrolyte channel is associated with many neuropsychiatric disorders including dementia. Investigators have reported the use of lorazepam and midazolam are the independent risk factors for the development of ICU delirium, which is consistent with our findings. The absence of sedation protocol explains this result; but sedation, especially benzodiazepine, was implicated in delirium several times. In a study, including trauma and post-operative patients, midazolam increased the risk of delirium by twofold to threefold; hence, many studies were conducted to find an alternative for midazolam. Dexmedetomidine seems to be the most attractive choice in current literature.

The risk of delirium is high in various diseases, for instance, hypertension, DM, myocardial ischemia, atrial fibrillation, peripheral vascular diseases, heart failure and COPD. This study underlined the presence of COPD as significant risk in the development of delirium in SICU. The most possible explanation is the occurrence of psychological disturbances caused by hypoxemia, hypercapnia and tobacco withdrawal. Furthermore, patients with COPD are frequently treated with corticosteroids, which is itself a risk factor for delirium but in this study, steroid association with delirium could not be ascertained. Most of the patients were prescribed intravenous hydrocortisone for the treatment of septic shock.

In the present study, we found that the risk of postoperative delirium in patients with electrolyte disturbances (hypernatremia; serum sodium >145) was higher than that of individuals with normal electrolytes. The result of this study is comparable to previous paper that described disturbance in sodium level was significant risk in the development of delirium in SICU. The most possible explanation is the occurrence of psychological disturbances caused by hypoxemia, hypercapnia and tobacco withdrawal. Furthermore, patients with COPD are frequently treated with corticosteroids, which is itself a risk factor for delirium but in this study, steroid association with delirium could not be ascertained. Most of the patients were prescribed intravenous hydrocortisone for the treatment of septic shock.

### Table 3 Sedative and analgesic medication as risk factor of delirium in univariate analysis

| Variables          | N=87 | Delirium (n=19) | OR (95% CI) | P value |
|--------------------|------|----------------|-------------|---------|
| Midazolam          |      |                |             |         |
| Yes                | 27   | 11 (40.7%)     | 4.46 (1.53 to 13.02) | 0.004*  |
| No                 | 60   | 8 (13.3%)      |             |         |
| Propofol           |      |                |             |         |
| Yes                | 36   | 13 (36.1%)     | 4.24 (1.42 to 12.60) | 0.007*  |
| No                 | 51   | 6 (11.8%)      |             |         |
| Analgesics         |      |                |             |         |
| Tramadol           |      |                | 0.199       |         |
| Yes                | 29   | 4 (13.8%)      | 0.46 (0.14 to 1.53) |         |
| No                 | 58   | 15 (25.9%)     |             |         |
| Nalbuphine         |      |                |             |         |
| Yes                | 18   | 5 (27.8%)      | 1.51 (0.46 to 4.95) | 0.493   |
| No                 | 89   | 14 (20.3%)     |             |         |
| Pethedine          |      |                |             |         |
| Yes                | 6    | 5 (83.3%)      | 23.93 (2.59 to 220.96) |         |
| No                 | 81   | 14 (17.3%)     |             |         |
| Morphine           |      |                | 0.502       |         |
| Yes                | 8    | 1 (12.5%)      | 0.48 (0.05 to 4.19) |         |
| No                 | 79   | 18 (22.8%)     |             |         |
| Fentanyl           |      |                | 0.105       |         |
| Yes                | 20   | 7 (35%)        | 2.46 (0.81 to 7.49) |         |
| No                 | 67   | 12 (17.9%)     |             |         |
| Steroid            |      |                |             |         |
| Yes                | 14   | 4 (28.6%)      | 1.55 (0.42 to 5.63) | 0.506   |
| No                 | 73   | 15 (20.5%)     |             |         |

### Table 4 Factors associated with delirium in multivariable logistic regression

| Variables         | P value | aOR   | 95% CI |
|-------------------|---------|-------|--------|
| COPD              | 0.003   | 55.02 | 4.60 to 745.67 |
| Pain ≥4           | 0.003   | 56.55 | 3.93 to 816.19 |
| Hypernatremia     | 0.007   | 40.73 | 2.80 to 592.27 |
| Sedation          | 0.072   | 8.71  | 0.82 to 91.89  |

Model accuracy=90.8%. Nagelkerke R²=69.4%.

### Table 5 Multivariable analysis of sedative medication as risk factor associated with delirium

| Variables         | P value | aOR   | 95% CI |
|-------------------|---------|-------|--------|
| Age (years)       |         |       |        |
| ≤40               | 0.142   | 2.53  | 0.74 to 8.7 |
| >40               | Ref     |       |        |
| Gender            |         |       |        |
| Male              | 0.296   | 0.46  | 0.11 to 1.96 |
| Female            | Ref     |       |        |
| BMI (kg/m²)       |         |       |        |
| ≥25               | 0.699   | 1.27  | 0.38 to 4.30 |
| <25               | Ref     |       |        |
| Midazolam         |         |       |        |
| Yes               | 0.002   | 7.37  | 2.04 to 26.61 |
| No                |         |       |        |
| Propofol          |         |       |        |
| Yes               | 0.003   | 7.02  | 1.92 to 25.76 |
| No                |         |       |        |

aOR, adjusted OR; BMI, body mass index.
The data from low-income and middle-income countries worldwide describing the prevalence of delirium are limited as most of the representation comes from Europe and high-income countries. What is the risk of delirium in low-income and middle-income countries? Not very much explicit from published papers. On this subject, these data can be a source of information related to the incidence of delirium to better understand its pattern and outcome. It will also help in designing appropriate future clinical studies.

This study has some shortcomings as it was a single-center study. Follow-up was restricted to 5 days only; therefore, we were not able to address the impact of delirium on long-term morbidity and mortality in our population. Delirium is managed with various ways (ie, physical restraint, sedatives, antipsychotics), and such diverse approaches may have impact on clinical outcomes. Also, delirium was measured as a dichotomous variable without taking into consideration the severity and duration. Considering that delirium is a predictor of mortality, prolonged cognitive impairment and higher cost of care, intervention studies should be conducted to determine whether alternative management strategies are associated with reductions in delirium and other short-term and long-term clinical outcomes in the critically ill population.

CONCLUSION
Delirium is a significant entity with poor outcome in SICU. Inadequate pain control, sedative medication, COPD, hypernatremia and fever are important modifiable risk factors, which should be controlled with appropriate management. More studies are warranted to confirm these findings in surgical group of patients distinctively.

Contributors AAA, MH, WA and MH developed the concept of study. AAA and SAR contributed to the study question and design. AAA, MH, WA, FK and BS contributed in literature search data analysis and interpretation; prepared the draft of the report and contributed to subsequent versions. AAA and BS contributed in drafting of the final report. MH, WA, AR and MF contributed to the data analysis and interpretation, and drafting of the final report. All authors approved the final version. AAA is the guarantor.

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Data availability statement Data are available on reasonable request.

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