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A Prospective Observational Cohort Study to Detect Occurrence, Risk Factors and Outcomes of Delirium in Intensive Care Unit

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Abstract:-

Background and objectives: Though common, delirium is frequently unrecognized in the Intensive Care Unit (ICU). There is no report on its incidence in our setting thus we aimed to find its incidence in ICU and the risk factors associated with it.

Material and Methods: This prospective observational cohort study was performed on 60 patients admitted for more than 24 hours in the BP Koirala Institute of Health and Sciences ICU from November 2018 to September 2019. Patients were evaluated for the presence of delirium by using the Confusion Assessment Method ICU scale every day 8 hourly during their stay in ICU. All possible risk factors associated with delirium were noted.

Result: The incidence of delirium was 41.7%. Also, 26.7% had mild to moderate delirium and 15% had severe delirium. Multivariate risk regression analysis revealed midazolam alone or with opioids (odds ratio [OR]=13.9, 95% confidence interval [CI]=1.48-130.68, p=0.02) and alcohol intake (OR=5.6, 95% CI=1-32.45, p=0.049) as independent risk factors for delirium. The patients with delirium had a significantly longer duration of mechanical ventilation (4[0-6.5] vs. 1[0–3] days), and length of ICU stay (11 [8-15] vs. 5 [4-9] days). But after adjusting for confounding variables for mortality at 30 days it showed delirium was not associated with mortality at 30 days.

Conclusion: Delirium is frequent in ICU. Midazolam and a history of alcohol intake are predictors of delirium in the ICU. Those patients with delirium had a longer duration of mechanical ventilation and increased ICU stay. However, it was not significantly associated with mortality at 30 days.

Keywords- *Delirium, incidence, risk factors, outcomes, Intensive care unit*

I. INTRODUCTION

Delirium in critically ill patients is a common occurrence, its incidence being 19 to 87% in intensive care units[1], [2]. It is an undervalued, commonly misdiagnosed problem in critically ill patients. Though recent advances in critical care medicine have improved the survival of critically ill patients, delirium remains one of the foremost unmet medical needs in healthcare.

Critically ill patients are subjected to various risk factors that lead to acute brain dysfunctions. The Diagnostic and Statistical Manual of Mental Disorders,4th (DSM-IV), lists four domains of delirium: disturbance of consciousness, change in cognition, development over a short period, and fluctuation[3]. Delirium has two wide ranges of presentation, hyperactive and hypoactive. Hyperactive delirium is characterized by aggression, impulsiveness, anxiety, sleeplessness, and hallucination and is prevalent only in 5-22 %.[4]. On the other hand, hypoactive delirium presents as inattention, lethargy, depression, and decreased level of consciousness without agitation. Due to a lack of recognition, hypoactive delirium is often missed and carries a bad prognosis.

Incidence of over 80% has been reported in critically ill patients[5]. The occurrence of delirium is greater in old age, those with pre-existing cognitive impairments, terminal illness, ventilated patients, alcoholism, and hypertension[5]–[7] Analgesia and sedatives used to relieve pain and anxiety in many ventilated patient also leads to delirium. The most common culprit is benzodiazepines. This usage of sedatives in turn masks the hypoactive delirium[5], [8], [9]. Delirium results in bad outcomes including prolonged mechanical ventilation, increased length of ICU stay, higher mortality, and higher hospital care. It also has long-term effects such as cognitive and functional deterioration[7], [10]. Thus it causes a significant economic burden in the hospital care system.

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Because of its increased incidence and unfavorable outcomes on patients' prognosis, the evaluation and identification of this clinical condition by health practitioners are important in the context of the intensive care unit.

Thus, the present study helps to find out the incidence of delirium in patients admitted to the ICU of our hospital (BPKIHS, Dharan, Nepal). We also assessed the various risk factors associated with our context. Along with this, we aimed to find out the patients' outcomes in terms of the total duration of ventilation, length of ICU stays, length of hospital stays, and mortality at 30 days through telephone communication.

II. RESEARCH METHODOLOGY

A prospective observational cohort study was conducted in the ICU of BPKIHS, Dharan, Nepal over 10 months from November 2018 to September 2019. and followed at 30 days. Ethical clearance was obtained from the Institutional Review Committee of BPKIHS, Dharan (IRC/1370/018) on 13th November 2018. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines were followed to report this study[11]

Before commencing the study, a pilot study was done to translate the CAM-ICU questionnaire of feature 4 into a Nepalese version, following guidelines according to international standards [12]. All sets of the questionnaire were translated into Nepali and back to English with the help of independent experts. The questionnaire was pretested among 30 nurses and residents they were asked to rate each item on the scale as to whether it was easily understandable or not. A good agreement (k=0.82) was achieved among the experts. Inter-rater agreement exceeded 90% on each item.

Both informed and written consent was taken from patients or patients' relatives, preferably first-degree relatives. All patients admitted in the medical or surgical ICU for more than 24 hours were enrolled. Patients who refused to give consent had a do-not-resuscitate order, were admitted to ICU after resuscitation for cardiac arrest, or those with neurological diseases and a history of psychiatric illness were excluded. All patients were managed according to our hospital ICU protocol. This study did not change our protocol in the management of patients.

Once the patients were admitted to ICU following data were collected: Age, gender, Body Mass Index (BMI), history of smoking and alcohol consumption, Charlson co-morbidity index, Glasgow Coma Scale (GCS) at the time of presentation, Simplified Acute Physiological Score(SAPS-II) at the time of ICU admission, ICU admission diagnosis. Co-morbidites such as Hypertension(HTN), Diabetes Mellitus(DM), Chronic obstructive pulmonary diseases(COPD), metabolic derangement such as [deranged Liver function test (LFT), Acute Kidney Injury (AKI, acidosis, features of sepsis] and drugs used in ICU (vasopressor and sedation) were also recorded.

Patients were evaluated every day 8 hourly by nursing staff and duty doctors using the Richmond Agitation Sedation Scale (RASS) for sedation assessment and delirium status via the CAM-ICU

Age was divided into two groups <60 years and ≥60 years group[13]. For sedation used in ICU, it was divided into four groups: midazolam alone or with opioids, opioids alone, non-opioids or non-benzodiazepines, and no sedation group.

The total duration of ventilatory support, length of ICU stays, length of hospital stays, and mortality at 30 days were recorded. All enrolled patients were followed up 30 days after discharge for mortality via telephone communication. For the severity of delirium, we used the delirium severity scale CAM-ICU-7[14]

The main outcome of this study was to find the incidence of delirium in patients admitted to the ICU. Secondary outcomes were severity of delirium, risk factors, duration of ventilation, length of ICU stay, length of hospital stay, and mortality at 30 days.

The sample size estimation was based on a previous study[15] which reported the incidence of delirium among critically ill patients as 50% and with a permissible error of 20% sample size was 96 but based on a medical record, and the total number of cases admitted to ICU, the corrected sample size was 60. Non-probability purposive sampling technique was used.

Data were entered in Microsoft Excel 2016 and converted into a Statistical Package for social sciences (SPSS 11.5) for statistical analysis.

The normality of data was tested with the Shapiro-Wilk test. Categorical data were expressed as numbers and percentage(%) and mean ± Standard deviation (S.D) / Confidence Interval (C.I.), median [Inter-quartile range (IQR)] for continuous data according to their distribution.

Following the CAM-ICU score, patients were divided into the "Delirious" and "Non-delirious" groups. For Categorical data, the chi-square test was used. For normally distributed continuous data, a student t-test was applied and for ordinal data, the Mann-Whitney U test was used to detect a difference between groups in the univariate analysis.

The risk factors associated with delirium were analyzed using univariate binary logistic regression. All possible factors with P<0.15 in the univariate binary logistic regression analysis were included in multivariate logistic regression analysis to find out the adjusted effect of all possible factors. The "Hosmer and Lemeshow goodness of fit test" was used to assess the fit of the model. A probability value (P) of <0.05 was considered significant.

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The outcome of delirium in terms of duration of mechanical ventilation, length of ICU stays, hospital stay, and mortality at 30 days was analyzed between delirious and non-delirious patients using the Mann-Whitney U test and Pearson chi-square test as applicable.

To assess whether delirium was associated with mortality at 30 days, logistic regression was done with all possible factors concerning mortality at 30 days and all possible factors with P<0.15 in the univariate binary logistic regression analysis were included in multivariate logistic regression analysis to find out the adjusted effect of all possible factors. A probability value (P) of <0.05 was considered significant.

III. RESULT

A total of 72 consecutive patients admitted to the ICU for more than 24 hours were assessed for eligibility from November 2018 to September 2019. Twelve patients were excluded because of varied reasons (five were admitted after cardiopulmonary resuscitation, four were admitted for neurological diseases and three had a history of psychiatric illness). The remaining 60 patients were assessed for delirium and risk factors associated with it and its outcomes (duration of mechanical ventilation, length of ICU stay, length of hospital stay, mortality at 30 days) Thebaseline characteristics of patients with and without delirium are presented in Table 1. Those patients with delirium had a history of alcohol intake [15 vs 9; P=0.008],higher SAPS II score [30(17.5-36) vs 18(11-26); P=0.04] and had developed sepsis [15vs12; P=0.048].

Table 1: Baseline characteristics of patients with and without delirium. Values were expressed in number, mean ± SD, and median (IQR) and analyzed between delirious and non-delirious patients using the Pearson Chi-square test, student t-test, and Mann-Whitney U test respectively

Characteristics		Non-Delirious patients (n=35)	Delirious patients (n=25)	p-value
Age groups (years)	<60/ ≥60	29/6	15/10	0.048
Gender	Male/female	18/17	17/8	0.199
Reason for admission	Medical/surgical	17/18	10/15	0.511
History	Alcohol	9	15	0.008
	Smoking	8	10	0.153
Comorbidity	COPD	3	3	0.663
	HTN	7	7	0.47
	DM	5	5	0.558
Developed Sepsis		12	15	0.048
SAPS II score (0-163 points)		18 (11-26)	30 (17.5-36)	0.04
GCS at time of ICU admission (3-15)		15 (10-15)	10 (10-14.5)	0.031
Charlson comorbidity index (0-37 points)		0 (0-2)	2 (0-3.5)	0.032
BMI (kg/m^2)		21.94 ± 2	22.4 ± 2	0.341
Metabolic factors	Deranged LFT	3	4	0.377
	AKI	12	11	0.445
	Acidosis	18	19	0.054
	Vasopressor required	24	17	0.963
Requirement of Mechanical ventilation		22	17	0.681

The incidence of delirium was 41.7%. (Fig 1) The delirium severity score CAM-ICU-7 was 58.3% never had delirium and 26.7% had mild to moderate delirium and 15% had severe delirium. In delirious patients, the delirium severity score [median(IQR)] was 4 (1-6).

Univariate analysis was used to assess the factors associated with delirium. Alcohol consumption [(OR=4.33, 95% CI=1.43-13.04, p=0.009)], Charlson co-morbidity index [(OR= 1.49, 95% CI = 1.06-2.08, p=0.019)], SAPSII score at time of ICU admission [(OR=1.07, 95% CI= 1.02-1.13, p= 0.006)] and midazolam alone or with opioids [Odds ratio; OR=10, 95% Confidence interval; CI= 2.45-40.7, p= 0.01] were found to be statistically significant. *Table 2.*

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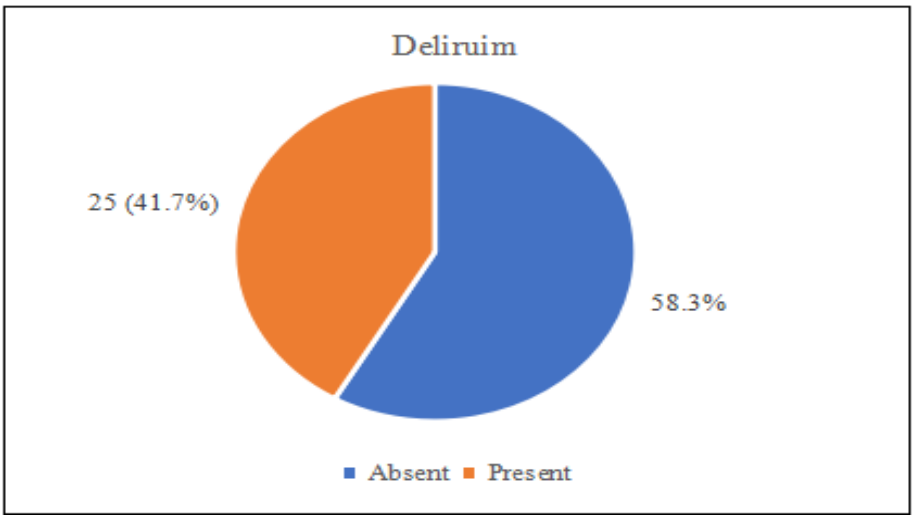

Fig. 1: Incidence of delirium.

Table 2: Univariate analysis of risk factors related to delirium

Variables		Standard Error (S.E.)	β beta (co-efficient)	Odd's ratio (OR)	95% Confidence Interval (CI)	P value
Age group* (≥60 years)		0.60	1.170	3.22	0.09-1.01	0.054
Male **		0.54	0.697	2	0.68-5.85	0.202
Alcohol		0.56	1.466	4.33	1.43-13.04	0.009
Smoking		0.57	0.811	2.25	0.73-6.92	0.157
SAPSII score		0.02	0.072	1.07	1.02- 1.13	0.006
GCS at ICU admission		0.08	-0.158	0.85	0.72-1	0.059
Charlson Co-morbidity Index		0.17	0.401	1.49	1.06-2.08	0.019
BMI (kg/m^2)		0.13	0.128	1.13	0.87-1.47	0.336
Sepsis		0.54	1.056	2.87	0.99-8.31	0.051
Co-morbidity	COPD	0.86	3.75	1.45	0.26-7.88	0.664
	HTN	0.61	0.442	1.55	0.46-5.18	0.472
	DM	0.69	0.405	1.50	0.38-5.86	0.56
Reason for admission	Surgery	0.52	0.348	1.07	0.38-3	0.895
	Medical	0.52	-0.348	0.93	0.33-2.62	0.895
Deranged LFT		0.81	0.709	2.032	0.41-10.01	0.384
AKI		0.53	0.409	1.50	0.52-4.32	0.446
Acidosis		0.57	1.096	2.99	0.96-9.27	0.058
Vasopressor		0.56	-0.026	0.97	0.32-2.93	0.963
Requirement of mechanical ventilation		0.22	0.553	1.256	0.42-3.75	0.681
Midazolam alone or with opioids		0.71	2.303	10	2.45-40.77	0.01
Opioids alone (fentanyl, morphine)		11147.5	-19.98	0.00	0.00	0.99
Non opioids and non benzodiazepines (ketamine, dexmedetomidine)		1.524	1.253	3.5	0.17-69.33	0.411

* in reference with patients age <60 years, ** in reference with female

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Multivariate logistic regression was used among factors with p<0.15 in univariate analysis to find out the adjusted effect of possible factors. Age group, GCS at time of admission, SAPS II score, Charlson co-morbidity index, alcohol intake, sepsis, acidosis, and sedation used in ICU were included in multivariate logistic regression. The Hosmer and Lemeshow goodness of fit test revealed model was fit (p=0.237). Multivariate logistic regression revealed midazolam alone or with opioids (OR= 13.9, 95%CI=1.48-130.685, p= 0.02) and alcohol intake (OR= 5.6, 95% CI= 1-32.45, p =0.049) were significantly associated with delirium after adjusting covariates. *Table 3, (Fig.2)*

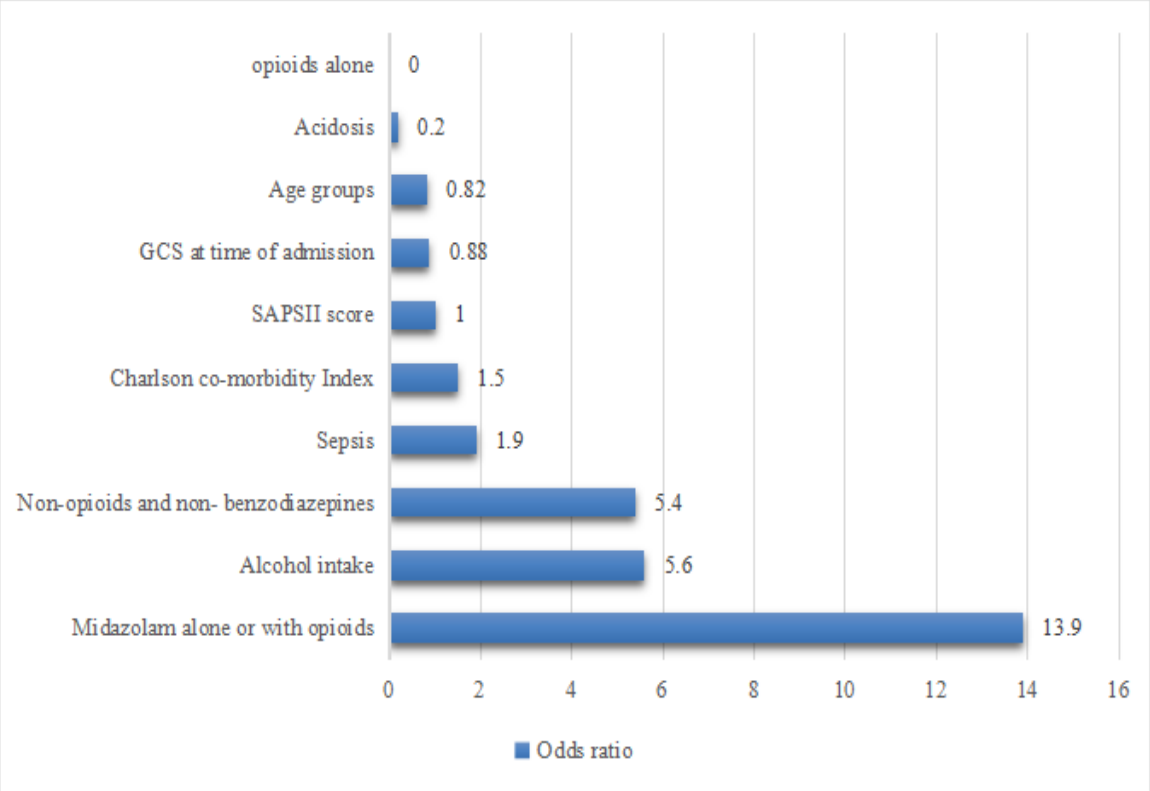

Fig. 2: Alcohol intake was significantly associated with delirium after adjusting covariates.

Table 3: Multivariate analysis of risk factors related to delirium

Variables	Standard error (S.E.)	β beta (co-efficient)	Odd's ratio (OR)	95% Confidence Interval (CI)	P value
Age groups (≥60 years)	1.29	0.196	0.82	0.06-10.35	0.87
GCS at the time of ICU admission	0.16	-0.11	0.88	0.63-1.23	0.48
SAPSII score	0.04	0.007	1.0	0.92-1.09	0.88
Charlson co-morbidity index	0.402	0.463	1.5	0.72-3.49	0.24
Alcohol intake	0.90	1.71	5.6	1.0-32.45	0.04
Acidosis	1.126	-1.54	0.2	0.02-1.93	0.17
Sepsis	0.915	0.67	1.9	0.32-11.81	0.46
Midazolam alone or with opioids	1.142	2.63	13.9	1.48-130.6	0.02
Opioids alone	9373.4	-21.1	0.00	0.00	0.99
Non-opioids and non-benzodiazepines	1.94	1.69	5.45	0.12-249.040	0.384

The patient with delirium had longer mechanical ventilation days [median (IQR) (4 [0-6.5] vs.1 [0–3]; P< 0.004)] and length of ICU stay (11 [8-15] vs. 5 [4–9]; P< 0.000). Duration of hospital stay was comparable between delirious and non-delirious patients. Table 4

Table 4: Outcomes between delirious and non-delirious patients. Values expressed in number and median (25th -75th IQR)

Outcomes	Delirious patients (n=25)	Non-delirious patients (n=35)	p-value
Duration of mechanical ventilation (days)	4 (0-6.5)	1 (0-3)	0.04
Length of ICU stay (days)	11 (8-15)	5 (4-9)	0.000
Hospital length of stay (days)	16 (11-20)	12 (7-20)	0.105
Mortality at 30 days	8	1	0.02

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Mortality at 30 days in delirious groups was 8 (32%) and in non-delirious patients was 1 (2.9%). To know the factors associated with mortality at 30 days, we have regrouped mortality at 30 days absent and present. All the factors such as patient characteristics like age, gender, presence of co-morbidity (COPD, HTN, DM), history of (alcohol use, smoking), the reason for admission, metabolic derangement (deranged LFT, AKI, feature of sepsis, acidosis), mechanical ventilation requirement and delirium were compared between two groups as mentioned above using the Pearson chi-square test. For BMI student t-test was applied. For GCS at the time of admission, the Charlson co-morbidity index and SAPS II score Mann Whitney U test were used.

Univariate binary logistic regression was used to assess the risk factors associated with mortality at 30 days. Delirium [OR= 16, 95% CI= (1.84-138.57), p= 0.0012], COPD [OR= 8, 95%CI= (1.30-48.95) p=0.024] and sepsis [OR= 5.42 95%CI= (1.02-28.78) p= 0.047] were significantly associated with mortality at 30 days.

The multi variate binary logistic regression was used among the risk factors associated with mortality at 30 days with p=<0.15 in univariate regression, COPD (OR=52.66, 95% CI= 1.34-2070.20, p=0.034) was the only independent risk factor for mortality at 30 days. Hence, delirium was not linked with mortality at 30 days.

IV. DISCUSSION

In this present study involving 60 patients, CAM ICU was used to assess delirium. More than one-third of enrolled patients were diagnosed to have delirium in the ICU of BPKIHS. The majority of delirious patients had mild to moderate delirium severity scores. The use of midazolam alone or in combination with opioids and a history of alcohol consumption were found to be strong predictors for the occurrence of delirium in our ICU. Our data also suggested that delirious patients had prolonged duration of mechanical ventilation and increased length of ICU stay. However, delirious patients did not have longer hospital stay when compared to non-delirious patients. Our study did not find any association of delirium with mortality at 30 days after adjusting for the confounding factors.

In the present study, the incidence of delirium was 41.7% which is higher than Ouimet etal[5] 31.8% and Tilouche etal[1]19% but lower than Ely et al[16] 81.7%. The low incidence in Ouimet etal(5) may be the use of the ICDSC checklist to define delirium which has low sensitivity and specificity of 74% and 81.9% compared to CAM ICU which has sensitivity and specificity of 80% and 95.5%[17]. On the other hand, Tilouche etal[1]evaluated patients for delirium only once in the morning every day but in this present study, patients have evaluated 8 hr every day so the chances of missing delirium were minimized. The higher incidence in Ely et al[16] evaluated mechanically ventilated patients only whereas the present study evaluated both ventilated and non-ventilated patients.

The present study reported two risk factors that were strongly associated with delirium; midazolam and alcohol consumption which was supported by many other studies. Tilouche etal[1] observed that the use of sedation (mainly midazolam and morphine) increased the risk of delirium by 5-fold. Similarly Irene. J. Zaal etal,[18] found that patients who were given benzodiazepines continuously developed delirium more frequently than compared to patients who were given benzodiazepines intermittently. Alcohol consumption was also an importantrisk factor in the development of delirium in our study which was homogeneous with a study conducted by M Kanova etal[19] and also Van Rompaey etal[6] conducted a multi-centered prospective cohort study in 523 patients aged more than18 years admitted to the ICU for more than 24h with Glasgow Coma Scale more than 10 to assess the risk factors associated with delirium which resulted from daily consumption of more than three units of alcohol was found to be a significant predictor of delirium. Ouimet et al[5] conducted a prospective study of 764 patients aged ≥18 years admitted to a medical-surgical ICU for more than 24h. Alcohol consumption was defined as two drinks or more daily, or weekly consumption of the equivalent of 26 oz of 40-proof alcohol. Similar to our finding alcohol consumption increased the risk for development of delirium by two-fold (OR=2.03, CI=1.2–3.2). However, we did not quantify the amount of alcohol consumption.

In our study,we found that the delirious patient had an increased duration of mechanical ventilation and also increased length of ICU stay which is consistent with other studies. Tilouche etal[1] found the duration of mechanical ventilation was extended by 8 days in delirious patients when compared to delirious patients. Similarly, Lin etal[20]observed that delirious patients had an increased duration of mechanical ventilation as compared to non-delirious patients.

Furthermore, events like self-extubation and removal of catheters (Foley's catheter, nasogastric tube, intravenous line) was more frequent with delirious patients[1], [21]. However, we did not assess these factors.

Regarding mortality at 30 days, our study did not find any association with delirium which was consistent withother studies. Thomason et al.[22] conducted a prospective cohort study of 261 consecutive patients admitted to the medical ICU but not requiring invasive mechanical ventilation during hospitalization. Similar to our findings, the authors found that hospital mortality was higher among patients who developed delirium (24/125 vs 8/135,). However, there was no significantrelationship between delirium and mortality after adjusting for multiple covariates In a prospective observational study of 275 mechanically ventilated patients, Ely etal[16] observed that delirious patients had an increase in 6-month mortality rates (34% vs 15%) even after adjusting for covariates. We included both ventilated and non-ventilated patients and assessed mortality only until 30 days. However, they enrolled only ventilated patients and followed the mortality for up to 6 months. These differences could be the reason for our contrasting findings.

Thus, critically ill patients are more susceptible to delirium because they usually have multiple system involvement and associated co-morbidity. Furthermore, the use of sedative medications and environmental factors in the ICU also plays a vital role in the development of delirium in these critically ill patients.

To focus on the limitation, this study was a single-centered prospective observational cohort study conducted in ICU patients only. Loss of follow-up bias is common in a prospective study. However, a loss of follow-up was not seen in our study. Doses and duration of sedation were not recorded, so we could not determinea dose relationship. Also, duration and sub-types of delirium were not evaluated.

V. CONCLUSION

In this study conducted in the ICU of BPKIHS, we found 41.7% of patients had delirium during their stay in the ICU. Alcohol intake and use of midazolam alone or with opioids were significantlyassociated with delirium. Delirium resulted in longer ICU stay, and prolonged mechanical ventilation but did not affect the total length of hospital stay. Mortality at 30 days was more in delirious patients (32% vs 2.9%). However, after adjusting all the confounding factors, delirium was not associated with mortality at 30 days.

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