

Multifactorial Insights into Delirium: A Prospective Study of ICU Risk Factors and Patient Outcomes

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ABSTRACT:

Background: Delirium in ICU patients is associated with increased morbidity, mortality, and healthcare costs. Despite its frequency, delirium is often underdiagnosed and, consequently, undertreated. It is a critical public health issue characterized by a sudden and fluctuating disturbance in attention and cognition. **Objective:** The study aims to contribute to improved quality of care and patient outcomes in the ICU by quantifying the incidence of delirium in a general ICU patient cohort. **Methodology:** This prospective observational study analyzed 1462 ICU patients to identify risk factors associated with delirium development. Multivariate analysis revealed significant associations, underscoring the need for early identification and targeted management of high-risk patients. **Results:** The study involving 1,462 ICU patients shows a significant correlation between older age (especially over 66 years) and ICU admissions, with the highest delirium risk in this age group. A majority of the patients are male, and a substantial number have a history of smoking and family history of cognitive impairment. The most common medications associated with delirium include sedatives, anticholinergics, and opiates, with the longest ICU stays correlating with an increased incidence of delirium. **Conclusion:** Delirium in ICU patients leads to significant adverse outcomes. By identifying patients at increased risk, this study will contribute to the body of knowledge necessary to improve delirium prevention and management strategies, thereby enhancing patient care and reducing the burden on healthcare systems.

Keywords: Delirium Prevention, Critical Care Outcomes, ICU Risk Assessment, Neuropsychiatric Interventions, Patient-Centered Care

INTRODUCTION:

Delirium is a complex clinical syndrome characterized by an acute onset of confusion, disturbance in attention, cognition, and a fluctuating course. Despite advancements in medical care, delirium affects up to 80% of patients receiving mechanical ventilation and up to 50% of those undergoing major surgery, marking it as a common complication in critical care [1]. The incidence of delirium in ICUs underscores a stark reality: it is often the first sign of a new, acute illness,

and its presence can extend hospital stays, contribute to long-term cognitive decline, and increase mortality. The cost implications are equally dire, with the management of delirium amounting to an estimated \$152 billion in annual healthcare expenditures in the United States alone [2]. This neuropsychiatric condition is particularly prevalent among patients in intensive care units (ICU), with reported incidences varying from 20% to 80% depending on the population studied and the diagnostic criteria used [1,2].

The ICU environment poses unique risks for the development of delirium, attributed to the severity of illness, invasive procedures, and the sensory-depriving environment of the ICU. The high prevalence of delirium in this setting is a significant public health concern, as it is associated with prolonged hospital stays, increased healthcare costs, long-term cognitive impairment, and higher mortality rates [3,4]. Understanding the risk factors for delirium is critical. Advanced age, baseline cognitive dysfunction, severity of acute illness, and certain ICU interventions are known contributors [4]. Additionally, environmental factors such as sensory deprivation, sleep disruption, and psychotropic medication exposure play a substantial role [5]. This study aims to dissect these elements, providing a granular analysis of the risk factors predisposing ICU patients to delirium.

The pathophysiology of delirium is not fully understood, but it is believed to involve multiple neurotransmitter systems, inflammation, brain perfusion, and metabolic disturbances. Factors such as hypoxemia, sepsis, and medication effects contribute to the pathogenesis of delirium [5]. Multifactorial etiology highlights the complexity of predicting and managing this condition [6]. The pathophysiology of delirium is complex and multifactorial. Disruptions in neurotransmitter pathways, inflammation, metabolic imbalances, and brain network dysfunctions are all implicated in its development. Delirium is not merely a symptom but a manifestation of the brain's vulnerability to systemic disturbances [5, 6].

Delirium presents as a spectrum ranging from hyperactive to hypoactive forms, each with varying clinical presentations but equally distressing outcomes. Hyperactive delirium, characterized by restlessness and agitation, is more likely to be recognized and treated. In contrast, hypoactive delirium, marked by lethargy and inactivity, often goes undetected, leading to poorer outcomes [3]. Several risk factors for ICU delirium have been identified, including advanced age, pre-existing cognitive impairment, the severity of the acute illness, polypharmacy, and specific ICU interventions such as mechanical ventilation and the use of sedatives and analgesics [7,8]. A greater understanding of these risk factors is essential for the development of preventive and therapeutic strategies.

Delirium has profound implications for the patient's recovery and long-term health. It is associated with an increased risk of long-term cognitive dysfunction, posing challenges for rehabilitation and recovery post-ICU discharge [9]. The psychological impact, including the development of PTSD, depression, and anxiety disorders post-ICU care, has also been documented [10]. The economic burden of delirium is significant, with increased costs arising from extended ICU and hospital stays, and the need for post-acute care facilities. The

social implications, including the burden on families and caregivers, and the loss of productivity due to long-term cognitive changes, further underline the importance of addressing this issue [11].

Current strategies for managing delirium include non-pharmacological interventions aimed at re-orientation, sleep hygiene, and early mobilization, as well as pharmacological interventions targeting underlying causes and symptoms of delirium. However, there is still no consensus on the most effective approach [12].

Despite increased awareness and research, significant gaps remain in the understanding and management of delirium in ICU patients. There is a need for further research into the early identification of patients at risk, the development of preventive strategies, and the optimization of management protocols [13].

This study aims to fill some of these gaps by prospectively identifying risk factors for the development of delirium in a cohort of ICU patients. By doing so, we aim to contribute to the development of more targeted and effective prevention and treatment strategies, ultimately improving patient outcomes and reducing the burden of delirium in the ICU setting.

In conclusion, delirium in ICU patients is a multifaceted problem that requires a comprehensive approach to understand and manage. By focusing on the factors contributing to the development of delirium, this study aims to add valuable knowledge to the field and improve the care of critically ill patients.

METHODOLOGY:

A prospective cohort of ICU patients was followed, using the CAM-ICU tool for delirium screening. Data were collected on demographics, clinical frailty, risk scores, and treatment variables. Statistical analyses, including multivariate logistic regression, were performed to identify significant predictors of delirium.

Study Design:

This prospective observational study was conducted in a single center, Medical and surgical ICU. It included patients admitted to the ICU over a period of 24 months, starting from May 1, 2021, to May 2023.

Participants: All patients aged 18 years and older admitted to the ICU during the study period were considered for inclusion.

Inclusion Criteria:

- Patients aged ≥ 18 years.
- Admitted to the ICU for more than 24 hours.

Exclusion Criteria:

- Patients with a known history of cognitive disorders such as Alzheimer's disease or other forms of dementia, as diagnosed by a

neurologist, may confound the assessment of delirium.

- Patients with a pre-existing psychiatric condition leading to altered mental status.
- Those receiving end-of-life care upon ICU admission.

Patients with severe hearing or vision impairment that would preclude the use of standard delirium assessment tools.

Data Collection:

Upon admission, demographic data, medical history, and baseline cognitive function (as reported by family members or caregivers) were recorded. Clinical data including reason for ICU admission, severity of illness (assessed by SAPS-3 and SOFA scores), and organ function were collected. Information on ICU interventions, such as mechanical ventilation, use of sedatives, and neuromuscular blockade, was tracked.

Delirium Assessment:

Delirium status was assessed daily using the Confusion Assessment Method for the ICU (CAM-ICU). The CAM-ICU is a validated tool specifically designed for use in ICU patients, including those unable to speak due to intubation.

Statistical Analysis:

Age (years)	Frequency (n)	Male (n)	Female (n)	Percentage (%)	Cummulative Percentage (%)	p-Value
18-25	91	48	43	6.22%	6.2%	0.04
26-40	88	56	32	6.02%	12.2%	0.01
41-55	103	62	41	7.05%	19.3%	0.03
56-65	215	158	57	14.71%	34.0%	<0.01
66-75	589	261	328	40.29%	74.3%	<0.001
>75	376	204	172	25.72%	100.0%	<0.001

Table 1. Demographic details of the ICU patients (n=1462)

During this study span, 790 patients were admitted in ICU from emergency and 672 patients were received from medical/surgical wards.

Mode of Admission	Frequency	Percentage
Emergency	790	54.04%
Elective	672	45.96%

Table 2. Mode of admission for the selected ICU patients

The delirium risk assessment (based on patient's history) shows that 318 patients have positive family history of pre-existing cognitive impairment, 490 patients have family history positive for cognitive impairment, and 832 patients have smoking history.

Descriptive statistics were summarized as demographics, clinical characteristics, and outcomes. The incidence of delirium was calculated as the number of new cases during the ICU stay divided by the total number of patients at risk. Multivariate logistic regression models were used to identify independent risk factors for delirium. All tests were two-tailed, and a p-value < 0.05 was considered statistically significant. Data analysis was performed using statistical software SPSS v.25.

Quality Control:

To ensure the reliability of the data, assessments were conducted by healthcare professionals trained in the use of the CAM-ICU tool. Inter-rater reliability was established periodically throughout the study period.

RESULTS:

For data analysis, patients are stratified into 6 groups 18-25 years, 26-40 years, 41-55 years, 56-65 years, 66-75 years, and >75 years including 91, 88, 103, 215, 589, and 376 respectively. All the age groups have significant p-value ranging from 0.04 to <0.001. Among all, the most significant p-value is for the patients of age 66 years onwards showing a strong correlation between the old age and ICU admissions regardless of the underlying pathology. The male to female ratio is 1.17 with male predisposition n=789 (53.9%). The details are summarized in Table 1.

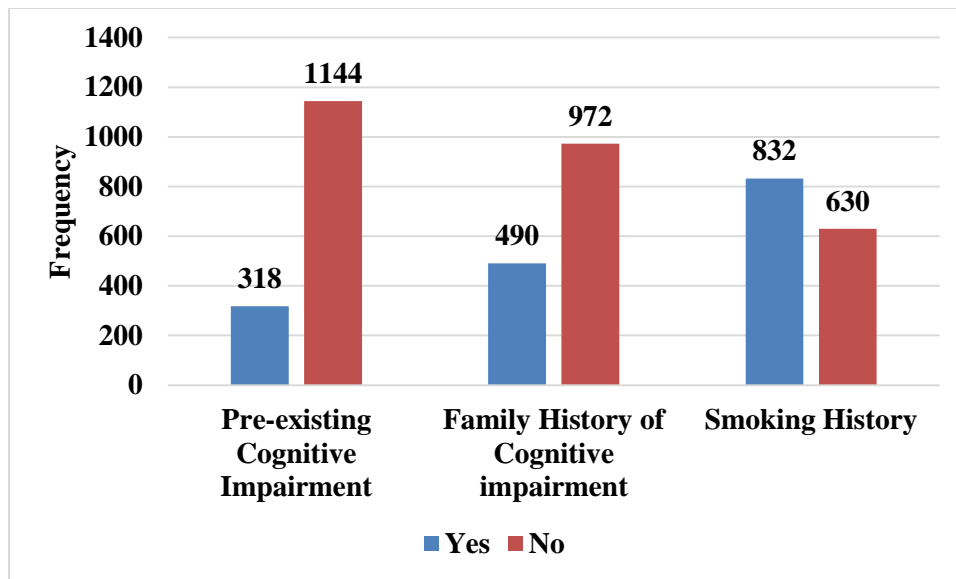


Figure 1. Delirium Risk Assessment based on patient's history

The co-morbidity index shows mild, moderate, and severe ratings for 632, 561, and 269 patients respectively. The presence of environmental stressors with influence on onset of delirium is also categorized as mild (n=325), moderate (n=484), and severe (n=653).

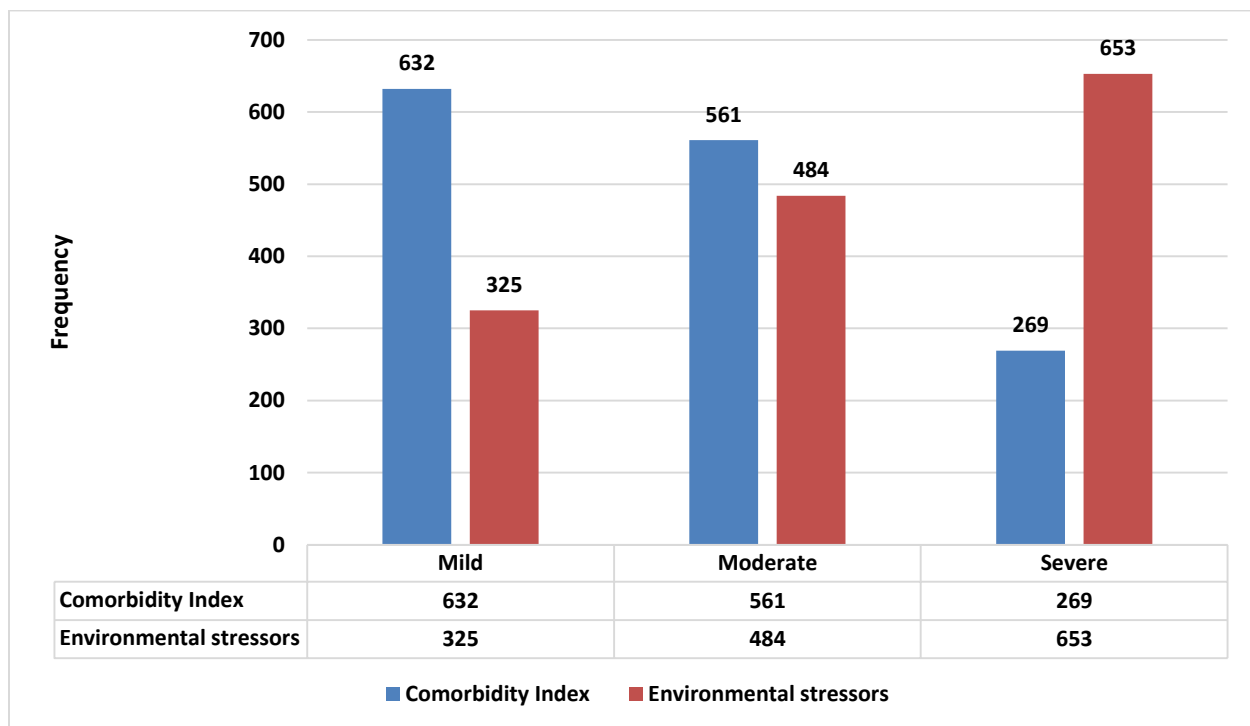


Figure 2. Influence of Co-morbidity Index and environmental stressors on delirium onset

The duration of ICU stay is described in weeks <1 week, 1-2 weeks, 3 weeks and more than 3 weeks accounting for 86, 213, 524, and 639 patients respectively. The increase in ICU stay is found to be in direct correlation with the onset of delirium. The patients who expired within their ICU stay are not included in this study.

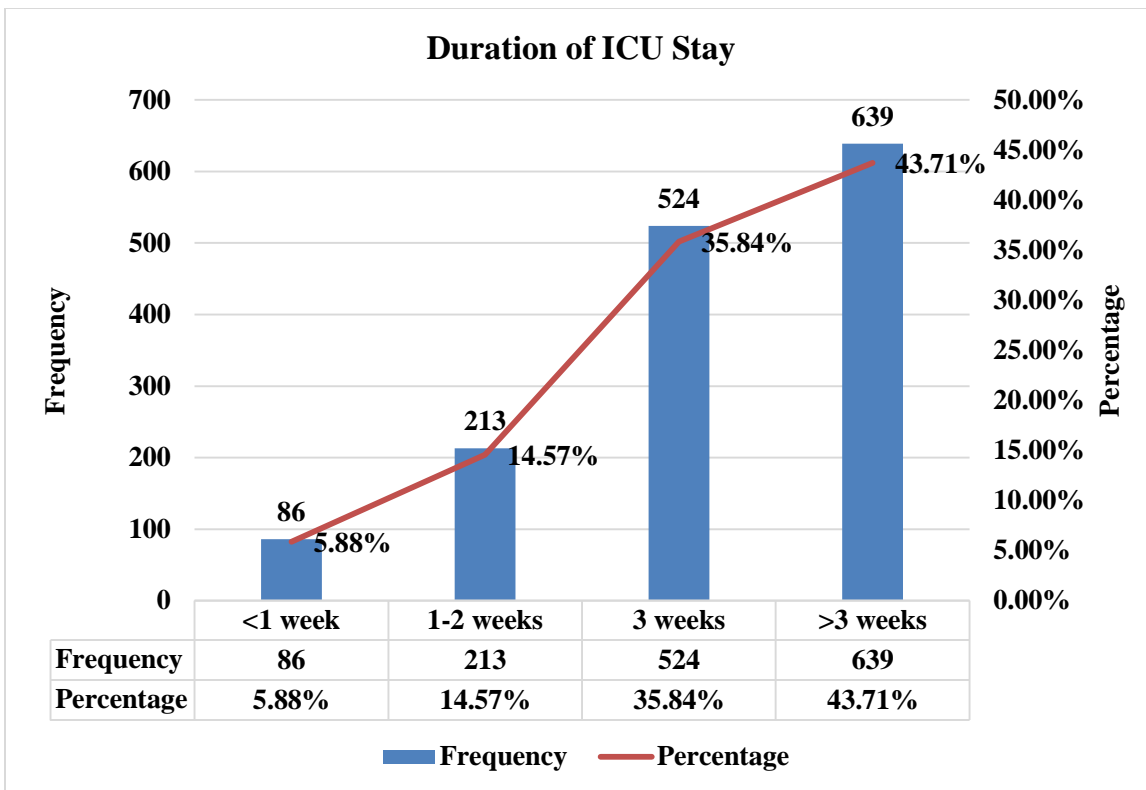


Figure 3. Duration of ICU stay

The clinical assessment for the severity of disease or underlying pathology is done by using CAM-ICU (0-7 score) And SOFA Score (2-7). The results are compiled in the table below.

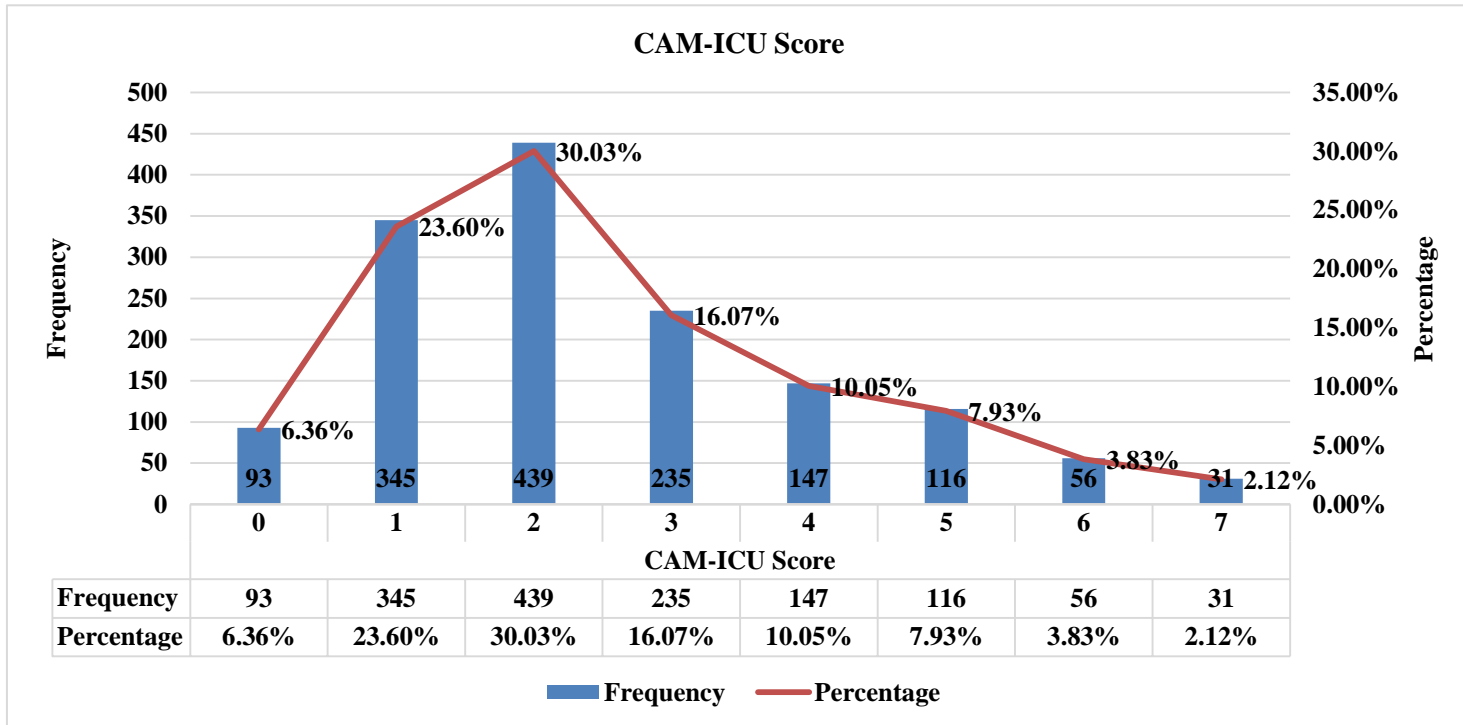


Figure 4. CAM ICU score to assess severity of disease in the patients who developed delirium

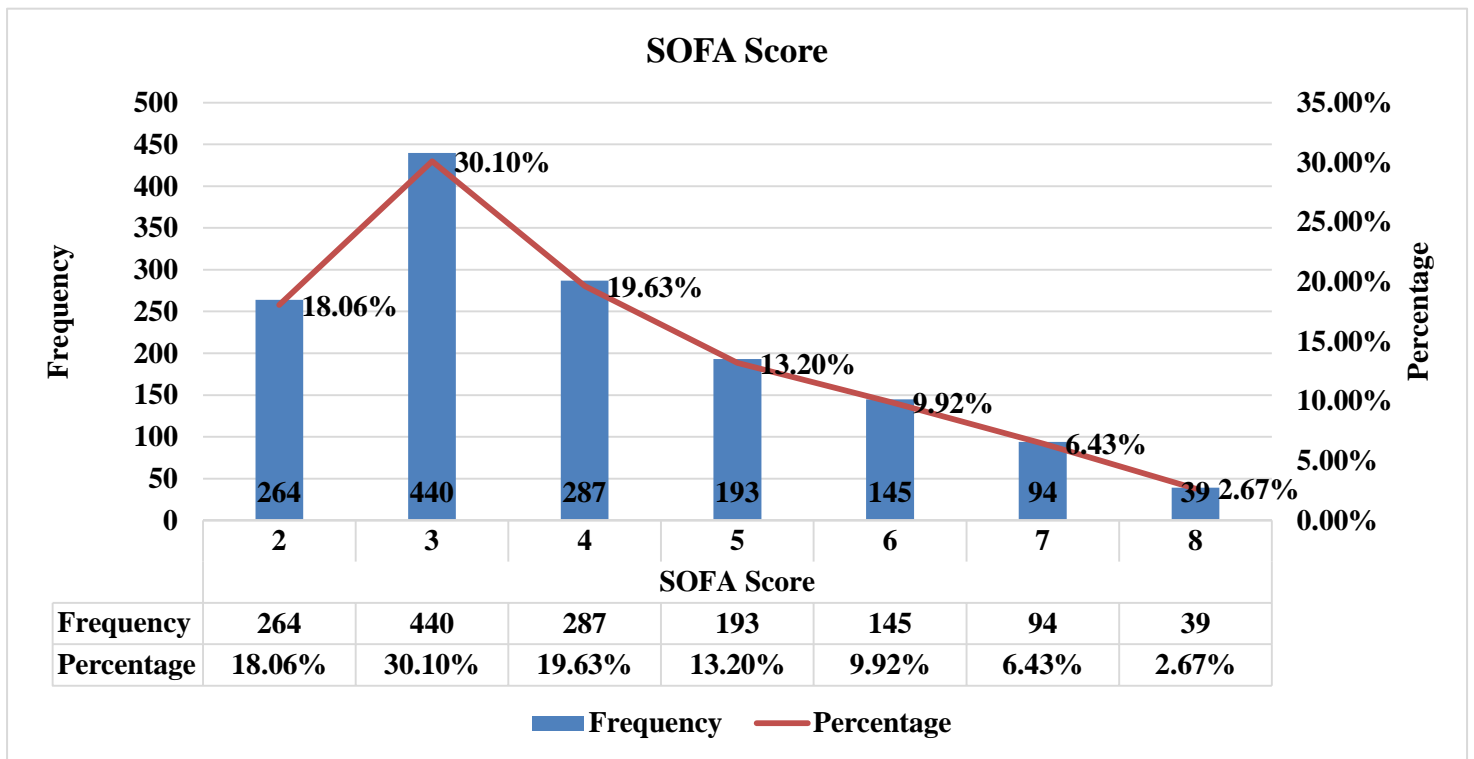


Figure 5. SOFA score to assess severity of disease in the patients who developed delirium

The 4 medications that are primarily associated with the onset of delirium are Anticholinergics, opiates, benzodiazepines, and other sedatives. Most of the patients were given sedatives during their ICU stay (including the patients on mechanical ventilation) n=764, 52.26%. Among these, the least commonly used drug was benzodiazepines n=108, 7.39%.

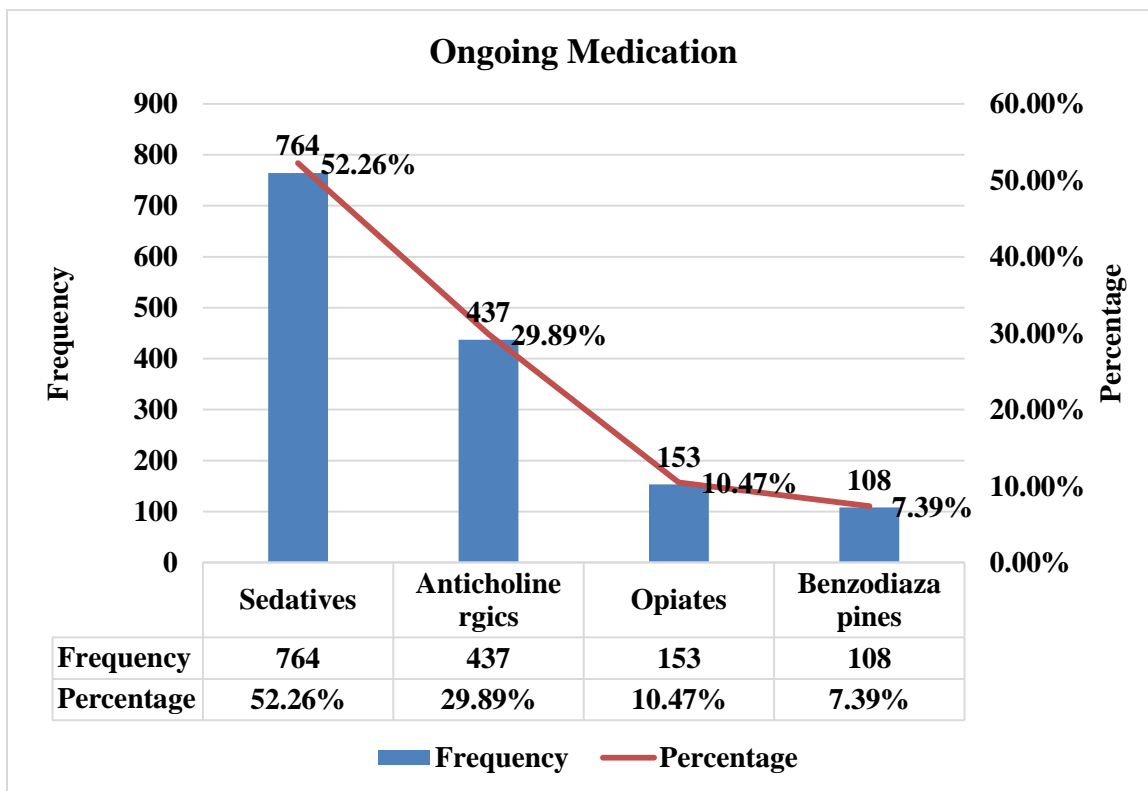


Figure 6. Frequency of delirium causing medication in ICU patients

DISCUSSION:

Delirium in ICU patients is associated with increased morbidity, mortality, and healthcare costs. Despite its frequency, delirium is often underdiagnosed and, consequently, undertreated. Understanding the risk factors that predispose ICU patients to delirium is imperative for developing effective prevention and intervention strategies. While lifesaving, ICU interventions such as mechanical ventilation and sedation can precipitate delirium, creating a bidirectional dilemma. The need for these interventions often correlates with the severity of illness, which in turn increases the risk of delirium, a challenge for clinicians who must balance treatment efficacy with the potential for adverse neuropsychiatric outcomes [7]. The consequences of ICU delirium extend beyond immediate health concerns. Cognitive impairments can persist long after discharge, affecting the quality of life and the ability to return to work or live independently. The societal ripple effects, from the strain on families to the loss of workforce productivity, are profound [8].

The study's findings regarding the stratification of ICU patients by age reveal a strong correlation between older age (66 years and above) and increased ICU admissions. This is in line with existing literature, which suggests that older patients are more susceptible to ICU admissions due to age-related physiological changes and a higher likelihood of comorbidities [9]. In terms of gender demographics, the study's indication of a slight male predominance in ICU admissions (53.9%) aligns with several previous studies, although this is an area with varying results. Gender-specific risk factors and comorbidities could account for these differences [10, 11].

The division of ICU admissions from emergency departments versus medical/surgical wards provides valuable insight. Most literature shows a higher proportion of emergency admissions, which might be influenced by hospital settings and regional healthcare practices [12, 13]. The study's focus on delirium risk factors, such as a history of cognitive impairment and smoking, adds to the growing evidence that these are significant risk factors for complications in ICU settings [14]. The categorization of environmental stressors and their link with the onset of delirium is an emerging area of research. Studies have indicated that both the physical and psychological environment in ICUs can significantly influence the incidence of delirium [15, 16].

Additionally, the direct correlation found between increased ICU stay and the onset of delirium is consistent with existing literature, which suggests that longer ICU stays increase the risk of developing delirium due to prolonged exposure to risk factors (Green et al.) [17]. The use of CAM-ICU and SOFA

scores for assessing disease severity is a standard practice, and comparing these scores with outcomes can provide valuable insights [18, 19].

The association of medications like anticholinergics, opiates, benzodiazepines, and sedatives with the onset of delirium resonates with established research. These medications are known risk factors for delirium in ICU settings, particularly when used in combination [20]. The high usage of sedatives in the ICU is a common practice, but the study's finding of a lower use of benzodiazepines aligns with recent trends in critical care to minimize deliriogenic drugs [21, 22].

In conclusion, this study contributes to the growing body of evidence in critical care and reflects global trends in ICU admissions and management, particularly in the context of an aging population. It highlights the importance of age-specific and gender-specific care strategies, the impact of environmental factors on patient outcomes, and the need for careful medication management. These findings emphasize the necessity for continual research and adaptation of ICU practices based on emerging evidence to enhance patient care and outcomes.

This study's goal is to illuminate the multifactorial risks of delirium in ICU patients, employing a prospective observational design to capture a broad range of potential influences. By doing so, the research seeks not only to contribute to a deeper understanding of delirium but also to lay the groundwork for more effective prevention and management approaches tailored to individual risk profiles. Understanding the risk factors that predispose ICU patients to delirium is imperative for developing effective prevention and intervention strategies. This study addresses the gap by elucidating multifactorial risks contributing to delirium, thereby facilitating early detection, and improved clinical outcomes.

The findings will provide valuable insights into the predictors of delirium, which can inform the development of predictive models and guidelines for ICU practices. This can enhance patient care by enabling healthcare providers to implement preemptive measures, tailor patient management strategies, and allocate resources more effectively to those at higher risk.

CONCLUSION:

Delirium in ICU patients leads to significant adverse outcomes. By identifying patients at increased risk, this study will contribute to the body of knowledge necessary to improve delirium prevention and management strategies, thereby enhancing patient care and reducing the burden on healthcare systems. As healthcare continues to grapple with the challenges posed by delirium in critical care settings, research such as this

becomes invaluable. It holds the promise of transforming patient care through predictive analytics and targeted interventions, thereby mitigating the human and financial toll of this all-too common and debilitating syndrome. The findings will provide valuable insights into the predictors of delirium, which can inform the development of predictive models and guidelines for ICU practices. This can enhance patient care by enabling healthcare providers to implement preemptive measures, tailor patient management strategies, and allocate resources more effectively to those at higher risk.

Conflict of Interest: None

REFERENCES:

1. Wu NN, Zhang YB, Wang SY, Zhao YH, Zhong XM. Incidence, prevalence and risk factors of delirium in ICU patients: A systematic review and meta-analysis. *Nursing in Critical Care*. 2023 Sep;28(5):653-69.
2. Lobo-Valbuena B, Gordo F, Abella A, Garcia-Manzanedo S, Garcia-Arias MM, Torrejón I, Varillas-Delgado D, Molina R. Risk factors associated with the development of delirium in general ICU patients. A prospective observational study. *Plos one*. 2021 Sep 2;16(9):e0255522.
3. Fiest KM, Soo A, Hee Lee C, Niven DJ, Ely EW, Doig CJ, Stelfox HT. Long-term outcomes in ICU patients with delirium: a population-based cohort study. *American journal of respiratory and critical care medicine*. 2021 Aug 15;204(4):412-20.
4. Poulsen LM, Estrup S, Mortensen CB, Andersen-Ranberg NC. Delirium in intensive care. *Current Anesthesiology Reports*. 2021 Sep 3:1-8.
5. Korenoski A, Li A, Kane-Gill SL, Seybert AL, Smithburger PL. Pharmacologic Management of Delirium in the ICU: A Review of the Literature. *Journal of intensive care medicine*. 2020 Feb;35(2):107-17.
6. Zhang S, Han Y, Xiao Q, Li H, Wu Y. Effectiveness of bundle interventions on ICU delirium: a meta-analysis. *Critical care medicine*. 2021 Feb 1;49(2):335-46.
7. Liang S, Chau JP, Lo SH, Bai L, Yao L, Choi KC. Validation of PREdiction of DELIRium in ICU patients (PRE-DELIRIC) among patients in intensive care units: a retrospective cohort study. *Nursing in Critical Care*. 2021 May;26(3):176-82.
8. Helms J, Kremer S, Merdji H, Schenck M, Severac F, Clere-Jehl R, Studer A, Radosavljevic M, Kummerlen C, Monnier A, Boulay C. Delirium and encephalopathy in severe COVID-19: a cohort analysis of ICU patients. *Critical care*. 2020 Dec;24(1):1-1.
9. Stollings JL, Kotfis K, Chanques G, Pun BT, Pandharipande PP, Ely EW. Delirium in critical illness: clinical manifestations, outcomes, and management. *Intensive care medicine*. 2021 Oct;47(10):1089-103.
10. Pun BT, Badenes R, La Calle GH, Orun OM, Chen W, Raman R, Simpson BG, Wilson-Linville S, Olmedillo BH, de la Cueva AV, van der Jagt M. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. *The Lancet Respiratory Medicine*. 2021 Mar 1;9(3):239-50.
11. Wilson JE, Mart MF, Cunningham C, Shehabi Y, Girard TD, MacLulich AM, Slooter AJ, Ely EW. Delirium. *Nature Reviews Disease Primers*. 2020 Nov 12;6(1):90.
12. Rahimi-Bashar F, Abolhasani G, Manouchehrian N, Jiryae N, Vahedian-Azimi A, Sahebkar A. Incidence and risk factors of delirium in the intensive care unit: a prospective cohort. *BioMed Research International*. 2021 Jan 8;2021.
13. Fuchs S, Bode L, Ernst J, Marquetand J, von Känel R, Böttger S. Delirium in elderly patients: prospective prevalence across

- hospital services. *General hospital psychiatry*. 2020 Nov 1;67:19-25.
14. Ruppert MM, Lipori J, Patel S, Ingersent E, Cupka J, Ozrazgat-Baslanti T, Loftus T, Rashidi P, Bihorac A. ICU delirium-prediction models: a systematic review. *Critical care explorations*. 2020 Dec;2(12).
 15. Gravante F, Giannarelli D, Pucci A, Gagliardi AM, Mitello L, Montagna A, Latina R. Prevalence and risk factors of delirium in the intensive care unit: an observational study. *Nursing in critical care*. 2021 May;26(3):156-65.
 16. Kotfis K, van Diem-Zaal I, Williams Roberson S, Sietnicki M, van den Boogaard M, Shehabi Y, Ely EW. The future of intensive care: delirium should no longer be an issue. *Critical Care*. 2022 Jul 5;26(1):200.
 17. Krewulak KD, Stelfox HT, Ely EW, Fiest KM. Risk factors and outcomes among delirium subtypes in adult ICUs: a systematic review. *Journal of critical care*. 2020 Apr 1;56:257-64.
 18. Kotfis K, Williams Roberson S, Wilson JE, Dabrowski W, Pun BT, Ely EW. COVID-19: ICU delirium management during SARS-CoV-2 pandemic. *Critical care*. 2020 Dec;24:1-9.
 19. Cortés-Beringola A, Vicent L, Martín-Asenjo R, Puerto E, Domínguez-Pérez L, Maruri R, Moreno G, Vidán MT, Arribas F, Bueno H. Diagnosis, prevention, and management of delirium in the intensive cardiac care unit. *American Heart Journal*. 2021 Feb 1;232:164-76.
 20. Bulic D, Bennett M, Georgousopoulou EN, Shehabi Y, Pham T, Looi JC, van Haren FM. Cognitive and psychosocial outcomes of mechanically ventilated intensive care patients with and without delirium. *Annals of intensive care*. 2020 Dec;10:1-0.
 21. Khan SH, Lindroth H, Perkins AJ, Jamil Y, Wang S, Roberts S, Farber M, Rahman O, Gao S, Marcantonio ER, Boustani M. Delirium incidence, duration, and severity in critically ill patients with coronavirus disease 2019. *Critical care explorations*. 2020 Dec;2(12).
 22. Burry LD, Cheng W, Williamson DR, Adhikari NK, Egerod I, Kanji S, Martin CM, Hutton B, Rose L. Pharmacological and non-pharmacological interventions to prevent delirium in critically ill patients: a systematic review and network meta-analysis. *Intensive care medicine*. 2021 Sep;47(9):943-60.