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ORIGINAL RESEARCH

Montelukast and Delirium Risk During Intensive Care Unit (ICU) Stay: Findings from a Cohort Study

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Background: Delirium is a frequent complication in critically ill patients and is associated with increased mortality, prolonged hospitalization, and long-term cognitive impairment. Montelukast, a leukotriene receptor antagonist commonly used in respiratory diseases, has been associated with neuropsychiatric adverse effects, including delirium. Evidence regarding its safety in critically ill adults is limited. This study aimed to investigate the association between montelukast use during ICU stay and the development of delirium and further evaluate its safety in the ICU.

Methods: This retrospective cohort study was conducted at King Abdulaziz Medical City, Saudi Arabia, between January 2018 and December 2021. Adult critically ill patients (18–79 years) who were admitted to ICUs for respiratory symptoms and categorized based on montelukast exposure during ICU stay. The primary outcome was assessing the incidence of delirium during ICU stay. Secondary outcomes included delirium duration, recurrence of delirium, delirium-free days, ventilator-free days, length of stay (LOS), safety outcomes (liver and kidney injury), 30-day and in-hospital mortality. Propensity score (PS) matching with a 1:4 ratio was performed to minimize baseline differences between the groups.

Results: Out of 1590 screened patients, 1469 were included, and 44 received montelukast during ICU stay. After PS matching (1:4), montelukast use was associated with a significantly higher incidence of delirium (OR 4.66, 95% CI 1.63 to 13.34; $P < 0.004$). Among patients who developed delirium, mixed delirium was the most frequent subtype in the montelukast group (50% vs 12.5% in controls). There were no notable differences found in terms of delirium-free days, recurrence of delirium, liver or kidney injury, length of stay, ventilator-free days, or overall mortality.

Conclusion: Our study demonstrates an association between montelukast use during ICU admission and a higher incidence of delirium. Prospective randomized studies are needed to confirm these findings.

Keywords: delirium, delirium-free days, montelukast, respiratory diseases, critical illness, intensive care unit, ICU

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Introduction

Delirium is common among critically ill patients, with incidence and prevalence rates ranging from 20% to 70%, depending on patient characteristics, setting, recognition methods, and the type of delirium.[1] The implications of delirium extend far beyond its acute presentation. It is linked to prolonged ICU and hospital stays, increased healthcare costs, and a higher risk of mortality.[2] Survivors often encounter long-term cognitive and functional impairments, with studies indicating a threefold increase in six-month mortality among ICU patients who experience delirium.[3] Furthermore, this condition significantly burdens healthcare systems as it prolongs recovery times and requires extensive post-discharge care.[4]

Despite significant advances in understanding delirium, the potential impact of various medications on its manifestation remains largely underexplored. Given the frequent overlap of delirium with respiratory conditions in critically ill patients, attention has turned to agents such as montelukast. Montelukast is a leukotriene receptor antagonist, commonly prescribed for asthma, allergic rhinitis, and exercise-induced asthma.[5] In addition to its respiratory benefits, observational studies suggest that montelukast may be linked to a reduced risk of developing dementia or a slower decline in cognitive function among patients with existing Alzheimer's disease.[6]

A recent study examining the impact of montelukast use before entering the ICU on in-hospital delirium incidence and prognosis in critically ill patients found that its use was significantly associated with reduced occurrences of delirium and lower 90-day mortality rates.[7] This suggests that montelukast may provide a potential therapeutic advantage in mitigating delirium. Despite its benefits, montelukast has been linked to an increased risk of neuropsychiatric events, including mood disorders such as anxiety and depression, sleep disturbances, and even aggression and suicidal thoughts in older adults.[8,9]

The risk of neuropsychiatric side effects has raised concerns among regulatory authorities. Since 2009, the US Food and Drug Administration (FDA) has mandated updated labeling for montelukast to highlight these risks.[10] This warning was prompted by postmarketing safety signals, which indicated a range of severe neuropsychiatric outcomes, including aggression, anxiety, depression, sleep-related issues, self-harm, committing suicide, and suicidal ideation.[8,9]

This raises an important question about the potential role of montelukast in the development of delirium among ICU patients. Critically ill patients are particularly susceptible to neuropsychiatric events due to severe underlying illnesses, organ dysfunction, sedation, benzodiazepine use, and use of inotropes or vasopressors.[11] Ongoing concerns persist regarding the safety of medications that may precipitate such adverse events, especially in this vulnerable population.[12] Although safety signals linking montelukast to neuropsychiatric complications have been reported in general populations, their relevance in the ICU setting has not been adequately investigated. Importantly, montelukast use may also reflect the presence of active or more severe underlying respiratory disease, such as asthma or chronic obstructive pulmonary disease, which themselves are independently associated with worse clinical outcomes and an increased risk of delirium in critically ill patients. In observational analyses, this introduces the possibility of confounding by indication, whereby the underlying condition prompting montelukast therapy, rather than the medication itself, may influence the risk of delirium. To address this gap, the present study aims to investigate the association between montelukast use during ICU stay and the development of delirium and to further evaluate its safety profile in critically ill patients.

Method

Study Design

A retrospective cohort study included adult critically ill patients aged 18–79 years who were admitted to the ICUs between January 2018 and December 2021. Patients diagnosed with asthma, chronic obstructive pulmonary disease (COPD), COVID-19, or interstitial lung disease (ILD) were identified using electronic health records. Eligible patients were categorized into two sub-cohorts based on exposure to montelukast during ICU admission. Montelukast exposure was defined as receipt of montelukast during an ICU stay, whether newly initiated in the ICU or continued from pre-ICU therapy. Exposure timing was limited to the ICU stay, and no predefined exposure window was specified. Dose and duration of montelukast therapy were not incorporated into the analysis. Patients were followed until hospital discharge or in-hospital death. The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) was used twice daily to assess the presence of delirium during the ICU stay. The study was carried out in line with the World Medical Association's Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects (originally adopted in 1964 and updated in 2013), along with relevant national ethical regulations and the guidance provided by the local institutions where the studies took place.

Study Participants

We screened adult critically ill patients aged between 18 and 79 years who were admitted to the ICUs for acute respiratory conditions, such as asthma exacerbations, COPD exacerbations, COVID-19, or interstitial lung disease (ILD), who stayed in the ICU for more than 48 hours. We excluded patients who had a known diagnosis of dementia, Alzheimer's, psychiatric disease, Down syndrome, or mental retardation, patients with liver disease, and patients with a history of drug abuse or alcoholism. We also excluded patients who required deep sedation (with a Richmond Agitation-Sedation Scale (RASS) score of −3 to −5) in the first 48 hours of ICU admission, as shown in Figure 1.

Study Setting

The study was conducted in all adult medical, surgical, trauma, and burn intensive care units (ICUs) at King Abdulaziz Medical City in Riyadh, Saudi Arabia. This facility is a tertiary-care academic referral hospital with over 1900 beds, offering a wide range of medical specialties for both adult and pediatric patients. The ICU has a capacity of more than 100 beds, including various specialized units. It operates as a closed unit, providing 24/7 coverage by board-certified intensivists in critical care. The multidisciplinary team consists of clinical pharmacy specialists, respiratory therapists, and nursing staff who participate in daily rounds.

Outcomes

This study aimed to investigate the association between montelukast use during ICU stay and the development of delirium, and further to evaluate its safety profile in critically ill patients. The primary outcome was assessing the incidence of delirium during ICU stay. The secondary outcomes included the duration of delirium, recurrence of delirium

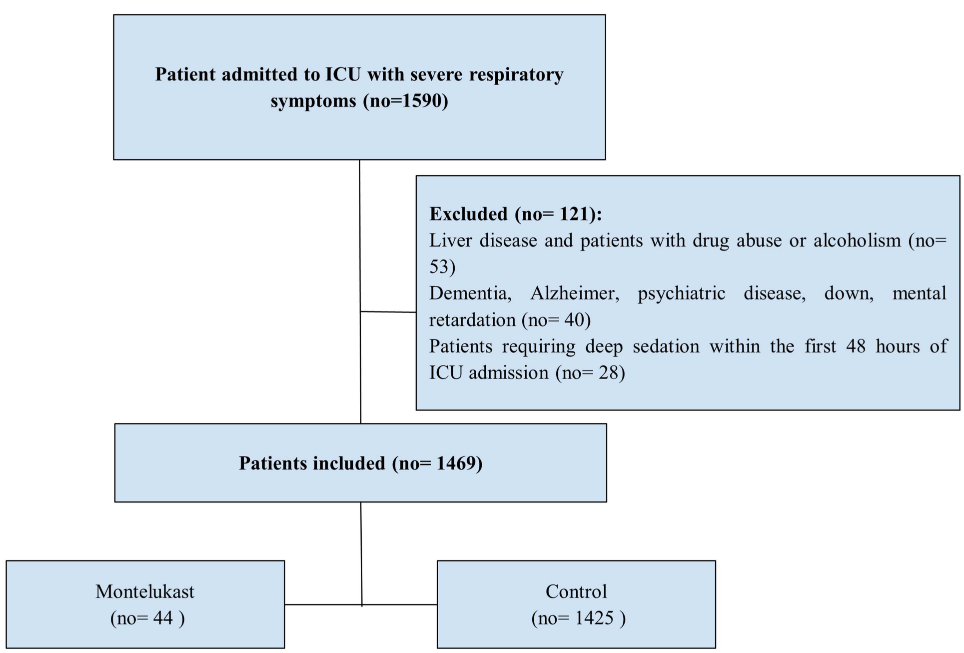

Figure 1 Eligibility Criteria Flow Diagram.

during ICU stay, delirium-free days, ventilator-free days, safety outcomes including acute kidney injury and liver injury during ICU stay, length of stay in ICU and hospital, as well as 30-day and in-hospital mortality.

Outcome's Definitions

- CAM-ICU score: confusion assessment based on the presence of two major criteria (acute or fluctuating onset and lack of attention) and at least one of the minor criteria (disorganized thinking or altered consciousness level), with the interpretation ranging from 0–7, with 7 being the most severe. CAM-ICU-7 scores were further categorized as 0–2: no delirium, 3–5: mild to moderate delirium, and 6–7: severe delirium.[13]
- RASS score: RASS is an instrument to assess sedation and agitation of adult ICU patients that is simple to use and has discrete criteria and sufficient levels for sedative medication titration and agitation evaluation with the interpretation ranging from +4 to −5: +4 is combative, +3 is very agitated, +2 is agitated, +1 is restless, 0 is alert and calm, −1 is drowsy, −2 is light sedation, −3 is moderate sedation, −4 is deep sedation, and −5 is unarousable.[14,15]
- Ventilator-free days (within 30 days): Calculated as follows: for patients who do not survive within 30 days, VFDs are recorded as zero. VFDs = 30 days after MV initiation (if the patient survives and is successfully liberated from MV). If a patient is alive but still on mechanical ventilation at the end of the period, their VFD score is also.[16]
- Delirium-free days: Define the number of days the patient was alive in the ICU without experiencing delirium.
- Delirium recurrence: Defined as the reappearance of delirium after it has previously resolved and defined as any positive delirium assessment following delirium clearance (48 hours of negative assessment after the initial delirium episode).
- Type of Delirium: Delirium is categorized into three different types:[17]
  - Hyperactive Delirium: Characterized by agitation, restlessness, and heightened alertness.
  - Hypoactive Delirium: Characterized by drowsiness, lethargy, and a reduced level of alertness.
  - Mixed Delirium: Involves features of both hyperactive and hypoactive delirium.
- Acute Kidney Injury (AKI): Defined as a sudden decrease of renal function within 48 hours, by an increase in absolute serum creatinine of at least 26.5 µmol/L (0.3 mg/dL) or by a percentage increase in serum creatinine ≥ 50% (1.5× baseline value) during ICU stay.[18]
- Liver Injury: Defined as if there is Alanine aminotransferase (ALT) elevated more than three times the upper limit of normal (ULN), or Alkaline phosphatase (ALP) elevated more than twice the ULN, or Total bilirubin elevated more than twice the ULN, along with increased ALT or ALP.[19]
- 30-day Hospital Mortality: Defined as a death occurring for any cause during 30 days of hospital stay.
- In-hospital mortality: Defined as death occurring for any cause during the hospital stay, patients who were discharged from the hospital alive were presumed to have survived.

Data Collection

Demographic data, including age, gender, BMI, comorbidities, and baseline laboratory data (eg, INR, aPTT, platelets, blood glucose level (BGL), CRP, D-dimer, ferritin, CPK, eGFR, serum creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT)) were collected. In addition, baseline severity scores such as SOFA scores, AKI status, GCS score, RASS score, MV status, PaO2/FiO2, FiO2, and VIS score within 24 hours of ICU admission were recorded for eligible patients.

The Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) score was assessed twice daily, once per shift, by a trained nurse to evaluate patients for delirium. The CAM-ICU assessment includes evaluating for acute onset of mental status changes or a fluctuating course, inattention, disorganized thinking, and altered level of consciousness. The results were recorded to monitor the presence and severity of delirium during the ICU stay. Moreover, prior montelukast use, ICU montelukast use (dose and duration), complications during ICU stay (including acute kidney injury and liver injury), length of stay, ventilator-free days, mortality, and other outcomes were collected. Patient data were collected from the Electronic Medical Records (BestCare) and managed using Research Electronic Data Capture (REDCap®) software hosted by King Abdullah International Medical Research Center (KAIMRC).

Data Management and Statistical Analysis

Continuous data were expressed as means with standard deviations (SD) or as medians with lower quartile (Q1) and upper quartile (Q3), based on their distribution characteristics. Categorical variables were presented as counts with percentages. The baseline characteristics and outcome variables were compared between the two study groups using appropriate statistical methods: a *t*-test for normally distributed variables and the Mann–Whitney *U*-test for those that were not normally distributed. For comparisons of binary or categorical data, either the Chi-Square test or Fisher's exact test was employed, depending on the data type.

The propensity score matching method was used to align patients who received montelukast, either started during their admission for exacerbation or continued as a home medication (Active group), with those who did not receive it during their ICU stay (Control group). This matching was done using a 1:4 ratio (Proc PS match). These propensity scores were generated through a greedy nearest-neighbor approach based on clinically and statistically relevant factors such as age, SOFA score, history of stroke, depression, and AKI at admission. Following this, regression analyses were conducted on the study outcomes, incorporating the propensity scores as covariates in the model.

For the analysis, multivariable linear regression, negative binomial regression, and logistic regression were employed as suitable, with odds ratios (OR) and estimates reported along with 95% confidence intervals (CI) as necessary. The Hosmer-Lemeshow goodness-of-fit test was used to evaluate how well the logistic regression model represented the observed data. No imputation was conducted for missing data since our patient cohort was not randomly selected. Statistical significance for all tests was determined at a p-value of less than 0.05, and SAS version 9.4 was used for all statistical analyses.

Results

Out of 1590 patients screened, 1469 were admitted to the ICU due to severe respiratory symptoms, of whom 44 received montelukast (10 mg/day) during their ICU stay. After propensity score matching (1:4 ratio), 42 patients treated with montelukast were matched with 168 control patients. Among patients in the montelukast group, 70.7% received the montelukast within 24 hours of ICU admission, 9.8% between 24–48 hours, and 19.5% after 48 hours. In the entire cohort prior to PS matching, the average age was 58.4 years (± 14.44), with males accounting for 57.2% of the patients, although males were more prevalent in the control group. The primary reasons for ICU admission included COVID-19 (67.9%), followed by respiratory failure/ARDS (Non-COVID-19) (27.8%), community acquired pneumonia (CAP) (5%), asthma exacerbation (4.4%), and exacerbation of COPD (3.7%).

The prevalence of asthma and COPD as comorbidities was significantly higher in patients who received montelukast compared to the control group. The montelukast group had a statistically significantly higher need for mechanical ventilation (MV) within 24 hours of ICU admission (68.5% vs 78.6) compared with the control group. On the other hand, the FiO2 requirement was significantly lower in the montelukast group (median FiO2 60.0 vs 47.5) compared with the control group. There were no significant differences in severity scores or C-reactive protein (CRP) levels between the two groups at ICU admission. After PS matching on predetermined variables, most differences were comparable, as shown in Table 1.

Delirium and Delirium-Related Outcomes

The incidence of delirium during the ICU stay was significantly high in the crude and regression analyses in the montelukast group (OR 4.66, 95% CI 1.63 to 13.34; $P < 0.004$). Among patients who developed delirium, mixed delirium was the most frequent subtype in the montelukast group (50% vs 12.5% in controls), followed by hypoactive delirium (25% vs 37.5%) and hyperactive delirium (25% vs 50%). The differences in delirium types between the groups were not statistically significant (P = 0.26). The median duration of delirium episodes was one day for both groups (**Beta Coefficient** –0.55, 95% CI –1.77 to 0.68; $P = 0.34$). Similarly, delirium-free days did not statistically significantly differ between the groups, with a median of 60 days in both the control and montelukast groups (P = 0.85). Regression analysis confirmed no association between montelukast use and delirium-free days (**Beta Coefficient** −0.00, 95% CI −0.07 to 0.06; P = 0.90). The difference in the recurrence of delirium during the same ICU admission was observed more often in the control group (OR 0.07, 95% CI 0.001 to 4.90; $P = 0.22$) (Tables 2 and 3).

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Table 1 Baseline Characteristics

Variable (s)	Baseline Characteristics- Pre-Matching				Baseline Characteristics- Post-Matching			
	Overall (no=1469)	**Control (no=1425)**	**Montelukast (no=44)**	**P-value**	**Overall (no=210)**	**Control (no=168)**	**Montelukast (no=42)**	**P-value**
Age, Mean (SD)	58.4 (14.44)	58.4 (14.47)	59.8 (13.60)	0.5787^	58.4 (15.06)	57.9 (15.37)	60.2 (13.77)	0.4021^
Male, n (%)	839 (57.2)	828 (58.1)	11 (25.0)	<0.0001^^	61 (29.0)	50 (29.8)	11 (26.2)	0.6484^^
BMI, Median (Q1,Q3)	30.1 (25.29, 35.20)	30.0 (25.23, 35.15)	32.4 (26.93, 37.33)	0.1293^	31.2 (26.56, 37.48)	30.9 (26.43, 37.47)	32.4 (27.02, 37.59)	0.5847^
SOFA Score, Baseline, Median (Q1, Q3)	4.0 (3.00, 7.00)	4.0 (3.00, 7.00)	4.0 (3.00, 6.00)	0.4718^	4.0 (3.00, 6.00)	4.0 (3.00, 6.00)	4.0 (3.00, 6.00)	0.8333^
Best GCS Baseline, Median (Q1, Q3)	15.0 (14.00, 15.00)	15.0 (14.00, 15.00)	15.0 (14.00, 15.00)	0.9128^	15.0 (15.00, 15.00)	15.0 (15.00, 15.00)	15.0 (14.00, 1 5.00)	0.3531^
RASS Score at Montelukast initiation, Median (Q1, Q3)	−1.0 (−3.00, 0.00)	–	−1.0 (−3.00, 0.00)	–	−1.0 (−3.00, 0.00)	–	−1.0 (−3.00, 0.00)	–
Patient received sedatives during ICU stay, n (%)	161 (68.2)	157 (70.1)	4(33.3)	0.0077**	24 (50.0)	20 (54.1)	4 (36.4)	0.3029^^
Serum creatinine (mmol/l), Median (Q1, Q3)	82.0 (64.00, 128.00)	82.0 (65.00, 129.00)	68.0 (57.00, 87.00)	0.0028^	75.0 (62.00, 103.00)	77.5 (62.00, 108.00)	68.0 (57.00, 87.00)	0.0551^
BUN, Median (Q1, Q3)	7.0 (4.70, 12.20)	7.0 (4.70, 12.30)	6.0 (3.70, 8.40)	0.0117^	6.3 (4.00, 9.80)	6.3 (4.10, 10.60)	6.3 (3.90, 8.50)	0.4754^
AKI at ICU admission, n (%)	329 (22.6)	324 (23.0)	5 (11.6)	0.0801^^	33 (15.8)	28 (16.7)	5 (12.2)	0.4814^^
Mechanical ventilation within 24 hours of ICU admission, n (%)	1002 (68.8)	969 (68.5)	33 (78.6)	0.1643^^	149 (71.6)	117 (69.6)	32 (80.0)	0.1916^^
FIO2 Requirement, Median (Q1, Q3)	60.0 (40.00, 85.00)	60.0 (40.00, 85.00)	47.5 (30.00, 80.00)	0.0509^	60.0 (35.00, 80.00)	60.0 (39.00, 80.00)	50.0 (35.00, 80.00)	0.4469^
International Normalized Ratio (INR), Median (Q1, Q3)	1.1 (1.00, 1.19)	1.1 (1.00, 1.19)	1.1 (1.00, 1.16)	0.8953^	1.1 (0.99, 1.15)	1.1 (0.98, 1.15)	1.1 (1.00, 1.16)	0.3830^
Platelets count, Median (Q1, Q3)	245.0 (184.00, 327.00)	243.5 (182.00, 326.00)	284.5 (220.00, 347.00)	0.0279^	262.5 (200.00, 344.00)	261.0 (197.00, 344.00)	275.0 (220.00, 336.00)	0.2195*
Blood Glucose Level, Median (Q1, Q3)	10.7 (7.40, 16.00)	10.6 (7.40, 15.90)	11.9 (8.05, 17.55)	0.1861^	11.2 (7.30, 16.70)	11.0 (7.30, 16.60)	11.9 (8.40, 18.30)	0.3499^
Albumin, Median (Q1, Q3)	31.0 (28.00, 34.00)	31.0 (27.00, 34.00)	34.0 (31.00, 37.50)	<0.0001*	34.0 (30.00, 37.00)	34.0 (30.00, 37.00)	34.0 (31.00, 37.00)	0.6842^
Alanine Aminotransferase (ALT), Median (Q1,Q3)	34.0 (20.00, 56.00)	34.0 (21.00, 57.00)	21.5 (17.00, 36.50)	0.0033^	29.5 (18.00, 50.00)	31.0 (19.00, 54.00)	22.0 (17.00, 37.00)	0.0566^
Aspartate Aminotransferase (AST), Median (Q1, Q3)	45.0 (28.00, 71.00)	46.0 (28.00, 72.00)	31.0 (19.50, 40.00)	0.0004^	37.0 (24.00, 59.00)	38.0 (24.00, 63.00)	32.0 (20.00, 40.00)	0.0554^
C-reactive protein (CRP), Median (Q1, Q3)	295.2 (287.20, 304.00)	295.2 (287.10, 304.00)	297.1 (288.15, 304.65)	0.6179^	112.5 (50.50, 154.50)	119.0 (53.00, 158.00)	45.5 (15.00, 93.00)	0.1829^
Comorbidity, n (%)								
Asthma	178 (12.1)	150 (10.5)	28 (63.6)	<0.0001^	130 (61.9)	104 (61.9)	26 (61.9)	>0.9999^^

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COPD	80 (5.4)	72 (5.1)	8 (18.2)	0.0002**	16 (7.6)	8 (4.8)	8 (19.0)	0.0018**
Cancer	127 (8.6)	124 (8.7)	3 (6.8)	0.6615**	14 (6.7)	11 (6.5)	3 (7.1)	0.8900**
Chronic kidney disease	191 (13.0)	187 (13.1)	4 (9.1)	0.4335^^	21 (10.0)	17 (10.1)	4 (9.5)	0.9084**
Diabetes mellitus	809 (55.1)	787 (55.2)	22 (50.0)	0.4923^^	110 (52.4)	90 (53.6)	20 (47.6)	0.4897^^
Hypertension	820 (55.8)	799 (56.1)	21 (47.7)	0.2724^^	123 (58.6)	102 (60.7)	21 (50.0)	0.2074^^
Heart Failure	153 (10.4)	148 (10.4)	5 (11.4)	0.8344**	25 (11.9)	20 (11.9)	5 (11.9)	>0.9999^^
Atrial fibrillation	89 (6.1)	85 (6.0)	4 (9.1)	0.3920**	25 (11.9)	21 (12.5)	4 (9.5)	0.5942^^
Admission Diagnosis								
Asthma exacerbation, n (%)	65 (4.4)	35 (2.5)	30 (68.2)	<0.0001**	52 (24.8)	24 (14.3)	28 (66.7)	<0.0001^^
COPD exacerbation, n(%)	54 (3.7)	45 (3.2)	9 (20.5)	<0.0001**	13 (6.2)	4 (2.4)	9 (21.4)	<0.0001**
COVID19, n (%)	997 (67.9)	986 (69.2)	11 (25.0)	<0001^^	110 (52.4)	99 (58.9)	11 (26.2)	0.0001^^
Respiratory failure/ARDS (Non-COVID19), n (%)	408 (27.8)	398 (27.9)	10 (22.7)	0.4479M	62 (29.5)	52 (31.0)	10 (23.8)	0.3640^^
Community Acquired Pneumonia (CAP), n (%)	74 (5.0)	71 (5.0)	3 (6.8)	0.5835**	9 (4.3)	6 (3.6)	3 (7.1)	0.3067**
Hospital Acquired Pneumonia (HAP), n (%)	12 (0.8)	10 (0.7)	2 (4.5)	0.0053**	4 (1.9)	2 (1.2)	2 (4.8)	0.1299**
Heart Failure exacerbation, n(%)	17(1.2)	16(1.1)	1 (2.3)	0.4824**	4 (1.9)	3 (1.8)	1 (2.4)	0.8007**
Sepsis/Septic shock, n (%)	80 (5.4)	72 (5.1)	8 (18.2)	0.0002**	18 (8.6)	10 (6.0)	8 (19.0)	0.0067**
Others, n(%)	198 (13.5)	194 (13.6)	4(9.1)	0.38694	31 (14.8)	28 (16.7)	3 (7.1)	0.1196^^

Notes: **T*-Test/^Wilcoxon rank sum test is used to calculate the P-value. ^ Wilcoxon rank sum test is used to calculate the P-value. ^^Chi-square test is used to calculate the P-value. **Fisher's Exact test is used to calculate the P-value.

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Table 2 Study Outcomes After PS Matching

	Control (N=168)	Montelukast (N=42)	P-value	Odd Ratio (OR)(95% CI)	P-value
Delirium, n (%)	8 (4.8)	8 (19.0)	0.002**	4.66 (1.625,13.342)	0.004
Hospital Mortality, n (%)	36 (21.8)	10 (25.0)	0.66^^	1.21 (0.517,2.818)	0.66
30-day Mortality, n (%)	26 (16.1)	7 (17.5)	0.84^^	1.09 (0.423,2.836)	0.85
Liver injury, n (%)	8 (4.8)	2 (4.8)	>0.99**	0.94 (0.189,4.717)	0.94
Acute kidney injury (AKI), n (%)	19 (11.3)	4 (9.5)	0.74**	0.87 (0.275,2.738)	0.81
Delirium recurrence, n (%)	3 (50.0)	1 (12.5)	0.12**	0.07 (0.001,4.898)	0.22
				Beta Coefficient (Estimate) (95% CI)	
Duration of first delirium episode, Median (IQR)	1.0 (1.00, 2.00)	1.0 (0.50, 2.00)	0.78^	−0.55 (−1.77,0.68)	0.34
Delirium Free Days, Median (IQR)	60.0 (60.00, 60.00)	60.0 (60.00, 60.00)	0.85^	−0.00 (−0.07,0.06)	0.90
Ventilator Free Days (30-day), Median (IQR)	23.0 (10.00, 26.00)	25.0 (15.00, 29.00)	0.156^	−0.14 (−0.46,0.18)	0.39
Duration of mechanical ventilation/ Intubation, Median (IQR)	63.8 (22.50, 212.65)	171.7 (118.80, 482.00)	0.16^	1.00 (0.998,1.010)	0.22
Duration of sedative agents infusion, Median (IQR)	68.0 (15.50, 204.00)	153.7 (122.00, 326.15)	0.12^	1.00 (0.997,1.009)	0.33
ICU Length of Stay, Median (IQR)	8.0 (5.00, 16.00)	11.0 (7.00, 21.00)	0.09^	0.18 (−0.10,0.46)	0.21
Hospital Length of Stay, Median (IQR)	15.5 (10.00, 25.00)	16.5 (11.00, 29.00)	0.28^	0.10 (−0.18,0.38)	0.47

Notes: ^ Wilcoxon rank sum test is used to calculate the P-value. ^^Chi-square test is used to calculate the P-value. **Fisher's Exact test is used to calculate the P-value.

Table 3 Types of Delirium

	Pre-Matching				Post-Matching			
	Overall (no=1469)	**Control (no=1425)**	**Montelukast (no=44)**	**P-value**	**Overall (no=210)**	**Control (no=168)**	**Montelukast (no=42)**	**P-value**
Mixed delirium, n (%)	25 (17.4)	21 (15.4)	4 (50.0)	0.04**	5 (31.3)	1 (12.5)	4 (50.0)	0.26**
Hypoactive, n (%)	74 (51.4)	72 (52.9)	2 (25.0)		5 (31.3)	3 (37.5)	2 (25.0)	
Hyperactive (Agitated and Restless), n (%)	45 (31.3)	43 (31.6)	2 (25.0)		6 (37.5)	4 (50.0)	2 (25.0)	

Notes: **Fisher's Exact test is used to calculate the P-value.

Safety Outcomes

Liver Injury and Acute Kidney Injury (AKI)

After PS matching, the incidence of liver injury was comparable between the groups, with eight patients in the control group compared to two in the montelukast group (OR 0.94, 95% CI 0.189 to 4.717; $P = 0.94$). Furthermore, the rate of AKI was lower in the montelukast group, occurring in four patients (9.5%) versus 19 patients (11.3%) in the control group, though the difference was not statistically significant (OR 0.87, 95% CI 0.275 to 2.738; $P = 0.81$) (Table 2).

ICU-Related Outcomes

ICU and Hospital Length of Stay (LOS)

In a crude analysis, patients who received montelukast had a longer ICU and the hospital LOS compared to the control group. Nonetheless, this difference did not achieve statistical significance in the crude analysis, with an ICU length of stay median of 11 days compared to 8 days (P-value 0.09), and a hospital length of stay median of 16.5 days versus 15.5 days (P-value 0.28), respectively. Following PS matching, the montelukast group still exhibited a longer length of stay in the ICU and hospital, although the difference was not statistically significant.(Beta Coefficient 0.18, 95% CI −0.10 to 0.46; P = 0.21 and Beta Coefficient 0.10, 95% CI −0.18 to 0.38; P = 0.47, respectively) (Table 2).

Ventilator-Free Days (VFDs) and Mortality

The median ventilator-free days (VFDs) for the montelukast group was 25 days, while the control group had a median of 23 days. This difference was not statistically significant in either crude or regression analysis (Beta Coefficient -0.14; 95% CI -0.46 to 0.18; P = 0.39). Additionally, hospital mortality rates were 21.8% for the control group and 25.0% for the montelukast group (OR 1.21; 95% CI: 0.517 to 2.818; P = 0.66). For 30-day mortality, the control group had a rate of 16%, compared to 17.5% in the montelukast group (OR 1.09; 95% CI: 0.423 to 2.836; P = 0.85). None of these findings were statistically significant.(Table 2).

Subgroup Analysis for COVID-19

In the COVID-19 subgroup, the incidence of delirium was similar between patients who received montelukast (9.1%) and those who did not (7.4%) (p = 0.83). The most common delirium subtype in this group was hyperactive delirium (47.9%), followed by hypoactive (35.6%) and mixed (16.4%). There were no significant differences in delirium duration, delirium-free days, or mortality outcomes between the two groups. In addition, among non-COVID-19 patients, delirium occurred in 21.2% of those who received montelukast compared to 14.6% in controls (p = 0.3039). Moreover, there were no significant differences in the duration of delirium episodes, delirium-free days, or mortality outcomes between the groups (Table 4).

Discussion

In this retrospective cohort study, we examined the association between montelukast use and the development of delirium during ICU admission, we found that the use of montelukast during an ICU stay was associated with a significantly higher incidence of delirium. However, there was no significant difference observed in the in-hospital mortality and 30-day mortality.

In our study, 16 patients developed delirium, eight patients in the control group (4.8%) and eight patients in the montelukast group (19%). This difference was statistically significant and aligns with findings from other observational studies.[20,21] Paljarvi et al reported that montelukast exposure was significantly linked to an increased risk of neuropsychiatric symptoms, including generalized anxiety disorder, insomnia, and greater use of antidepressant medications, compared to non-exposed patients.[9] In contrast, Li et al investigated the association between pre-ICU montelukast exposure and the incidence of delirium, reporting that montelukast was associated with a reduction in in-hospital delirium.[7] This discrepancy may be attributable to differences in the baseline patient characteristics, as patients in the montelukast group in the Li et al study had significantly higher SAPS II, SAPS III, SOFA, and SIRS scores compared

Table 4 COVID-19 Subgroup Analysis of Delirium Incidence, Type, and Mortality Outcomes

Parameters	Overall COVID 19 (N=997)	Control COVID 19 (N=986)	Patients Received Montelukast, COVID-19 (N=11)	p-value	Overall Non-COVID-19 (N=472)	Control Non-COVID-19 (N=439)	Patients Received Montelukast Non-COVID 19 (N=33)	p-value
Delirium, n (%)	74 (7.4)	73 (7.4)	1 (9.1)	0.8319**	71 (15.0)	64 (14.6)	7 (21.2)	0.3039**
Hospital Mortality, n (%)	277 (28.1)	276 (28.3)	1 (10.0)	0.2001**	167 (36.7)	158 (37.4)	9 (28.1)	0.2964^^
30-day Mortality, n (%)	242 (24.7)	241 (24.9)	1 (9.1)	0.2269**	112 (25.2)	106 (25.6)	6 (19.4)	0.4394^^

Notes: ^^Chi-square test is used to calculate the P-value. **Fisher's Exact test is used to calculate the P-value.

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with controls. Although propensity score matching and regression models were utilized, residual confounding likely contributed to the observed association in their findings.[7]

Furthermore, subgroup analysis by COVID-19 status showed that COVID-19 infection was not associated with a statistically significant increase in delirium incidence among our critically ill patient, regardless of montelukast use. In the non-COVID-19 subgroup, montelukast-treated patients showed a higher proportion of mixed-type delirium and a lower proportion of hypoactive delirium compared to controls. These differences may reflect the potential neuropsychiatric influence of montelukast on central nervous system excitation and behavioral regulation through leukotriene pathway modulation.[22] Hypoactive delirium is reported as the most common subtype in the ICU, accounting for approximately half of all delirium cases among critically ill patients.[17] Consistent with this, hypoactive delirium was the predominant presentation in our cohort before matching. In the montelukast group, 50% of delirium cases were classified as mixed, compared with 12.5% in the control group, suggesting a higher prevalence of mixed delirium among montelukast users. This finding is consistent with previously reported neuropsychiatric adverse effects, including depression, aggression, and abnormal behavior, which were significantly frequently reported with montelukast.[8] Hypoactive delirium was the second most common subtype, occurring in 25% of cases in the montelukast group and 37.5% in the control group. The differences in delirium subtypes between the two groups reached statistical significance. Previous studies have not specifically examined the relationship between montelukast use and the occurrence of different delirium subtypes. Nonetheless, the associations between montelukast and prescriptions for antidepressants have been documented in other observational studies.[12,23] An observational study found a correlation between montelukast use and increased prescriptions for antidepressants.[12]

In our cohort, the median duration of delirium episodes was one day in both groups, and recurrence of delirium during the same ICU stay was comparable across groups. Despite this similarity, patients treated with montelukast had slightly longer ICU and hospital stays compared to the control group, although the difference was not statistically significant., which might suggest that montelukast use may be associated with a high incidence of neuropsychiatric symptoms that required increased duration of mechanical ventilation and use of sedative agent infusion compared to the control group.

Likewise, mortality outcomes in our study were not affected; in-hospital and 30-day mortality rates were comparable between groups, at 16% for the montelukast group and 17.5% for the control group. This aligns with previous reports showing control group mortality of 21.8% compared with 25% in the montelukast group.[7] Our finding aligns with prior studies reporting no significant benefit of montelukast on mortality or length of stay, despite some numerical differences.

Investigation of the occurrence of liver injury and acute kidney injury (AKI) shows no significant difference between the montelukast and the control groups. While the number of liver and kidney injury cases was lower in the montelukast group, these differences did not reach statistical significance upon further analysis. Overall, the incidence of both events was low across the groups. This finding is consistent with the established safety profile for montelukast.[24–27] However, it is important to highlight that montelukast-induced liver injury, although rare, is typically reported after weeks to months of therapy.[24,25] In our study, monitoring of montelukast usage was Montelukast use is likely a proxy for more active or severe underlying respiratory disease raising the possibility of residual confounding. Although our propensity score model incorporated age, SOFA score at ICU admission which includes a respiratory component and mechanical ventilation status as markers of overall and respiratory severity. However, the current propensity score matching strategy does not adequately distinguish whether delirium is associated with montelukast exposure itself or severe underlying respiratory disease.[24,25]

This study has several strengths, including adjustment for key baseline confounders using propensity score matching, comprehensive assessment of clinically relevant outcomes, and standardized delirium monitoring. Importantly, baseline markers of illness and respiratory severity, including SOFA score, early mechanical ventilation within 24 hours of ICU admission, and FiO_2 requirements, were not significantly different between groups, and non–COVID-19 respiratory failure/ARDS was numerically more frequent in the control group, although not statistically significant. Although the findings are biologically plausible and based on standardized delirium assessment using CAM-ICU, the novelty of the results is moderate, and the conclusions remain exploratory. On the other hand, the relatively small number of patients exposed to montelukast limits statistical power and precision of effect estimates. Additionally, residual confounding cannot be fully excluded given the observational design. Therefore, these findings should be interpreted cautiously and confirmed in larger, prospective studies

Conclusion

Our study found an association between montelukast use during ICU admission and a higher incidence of delirium. Given the observational nature of the study, causality cannot be inferred, and other clinical factors (eg, sedation exposure, mechanical ventilation, sepsis, and hypoxia) may contribute to this association. Future research should further investigate the link between montelukast and increased antipsychotic use in the ICU to improve treatment strategies and patient outcomes.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

The study was approved in May 2024 by the King Abdullah International Medical Research Center Institutional Review Board, Riyadh, Saudi Arabia (Ref.# NRC24R/122/03). Participants' confidentiality was strictly observed throughout the study by using anonymous unique serial numbers for each subject and restricting data only to the investigators. Informed consent was not required due to the research's method as per the policy of the governmental and local research center.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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