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Delirium in older persons

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Delirium in older persons

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Editorial: Delirium in older persons

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KEYWORDS

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Editorial on the Research Topic
Delirium in older persons

Delirium, a common yet often overlooked condition in the elderly, involves acute confusion and disorientation, often triggered by factors like infections, medications, and chronic illnesses. Delirium is frequently misdiagnosed or dismissed as normal aging, leading to delayed treatment and worse outcomes. Recognition and management are essential for improving quality of life, reducing hospital stays, healthcare costs, and the risk of long-term cognitive decline. This editorial explores biomarkers, medications, and assessment techniques to identify and reduce delirium.

Serum lactate

Serum lactate levels are vital in managing critically ill patients, especially in predicting intensive care unit (ICU) delirium and mortality. In this retrospective cohort study, "*Associations of serum lactate and lactate clearance with delirium in the early stage of ICU*", data from the MIMIC-IV database were analyzed to explore the link between lactate levels within 24 h of ICU admission and delirium, as well as lactate clearance rates and 30-day mortality (Qian et al.). Lactic acidosis or hyperlactatemia increased delirium risk, while decreased lactate clearance was associated with higher mortality. These results highlight the need to monitor and manage lactate levels.

Polypharmacy in Parkinson's disease (PD)

PD presents challenges, especially in older patients with polypharmacy. In the case report, "*Exacerbation of delirium and epileptic seizures in an older man with idiopathic Parkinson's disease due to multiple prescriptions*", an elderly male with PD and mild renal dysfunction was prescribed 14 medications. He developed delirium and seizures, which improved after reducing his medication load, including amantadine (Yamaguchi et al.). This case highlights the importance of careful drug management in PD, urging clinicians to regularly reassess medications to prevent polypharmacy complications.

Intraoperative EEG monitoring

Postoperative delirium (POD) is a serious complication that can worsen patient outcomes, increasing morbidity, hospital stays, and long-term cognitive issues. The systematic review, "*Intraoperative electroencephalogram patterns as predictors of postoperative delirium in older patients*", analyzed 19 studies with 7,229 patients and found that intraoperative EEG patterns, especially burst suppression, increased the risk of POD by 41% (Likhvantsev et al.). This highlights the importance of EEG monitoring during surgery in older patients, offering a potential tool for early detection and prevention strategies to improve outcomes and reduce POD risk.

Plasma visfatin

Visfatin, a pro-inflammatory cytokine, plays a dual in POD. In the prospective analysis, "*Preoperative plasma visfatin may have a dual effect on the occurrence of postoperative delirium*", elderly patients scheduled for hip fracture surgery were monitored. Preoperative plasma visfatin levels below 37.87 ng/ml were protective against POD, whereas levels exceeding this threshold increased the risk; an effect mediated by elevated postoperative IL-6 levels (Kang et al.). These findings suggest that preoperative monitoring may help manage POD risk.

Preoperative anticholinergics

Anticholinergics, used to treat muscle spasms, overactive bladder, and respiratory or gastrointestinal disorders, can increase delirium risk. In the secondary analysis of the randomized, prospective, multicenter study, "*Anticholinergic drug exposure increases the risk of delirium in older patients undergoing elective surgery*", found that among 899 elderly surgical patients, a higher preoperative anticholinergic burden, measured by the Anticholinergic Risk Scale and Burden Score, was associated with a 2.7-fold increase in POD (Herrmann et al.). The study emphasizes the need to adjust medication regimens before surgery to reduce POD and improve outcomes.

Leveraging machine learning (ML)

Delirium is a common and serious issue in older ICU patients, leading to poor outcomes. In the study "*Interpretable machine learning model for early prediction of delirium in elderly patients following intensive care unit admission: a derivation and validation study*", researchers used ML to predict delirium risk in the MIMIC-IV database (Tang et al.). The XGBoost model, enhanced with SHapley Additive exPlanations, offered the most accurate and interpretable predictions. Key predictors included the Glasgow Coma Scale, mechanical ventilation, and sedation. This approach enables personalized risk assessment and could improve early intervention for elderly ICU patients.

Frailty index (FI) predicts delirium

Frailty, marked by reduced physiological reserve and higher vulnerability, increases the risk of adverse health outcomes like falls and mortality. In the article, "*Frailty index and risk of delirium in hospitalized patients: a two-sample Mendelian randomization study*", the authors explored the causal link between frailty and delirium (Chen et al.). Using genome-wide data, they found that a higher FI might raise delirium risk. This underscores the need for early frailty assessment in hospitalized patients.

Emergency department (ED) triage

Delirium is often overlooked in the ED. In the prospective diagnostic study, "*The 4AT scale for rapid detection of delirium in emergency department triage*", researchers evaluated the 4AT scale for its accuracy and efficiency in triage (Soler-Sanchis et al.). They examined 370 patients aged 65 and older, and found that a score ≥ 3 had an 85.1% sensitivity and 66.9% specificity in detecting delirium. The scale's use did not extend triage time, making it a valuable tool for early delirium detection without disrupting ED workflow.

Leveraging caregivers

Early detection of delirium in the ICU is vital for patient outcomes. The Sour Seven Questionnaire adapted into Chinese, was evaluated in the study, "*Translation, cultural debugging, and validation of the Chinese Version of the Sour Seven Questionnaire*" (Zhu et al.). Tested among families of ICU patients in China and compared with the Confusion Assessment Method for ICU, the questionnaire showed high sensitivity (86.3%) and specificity (97.4%). It proved reliable for caregiver screening of ICU delirium, even during online visits, enabling families to assist in early detection.

Preventing post-stroke delirium

Post-stroke delirium is a serious complication that affects recovery. In the prospective observational study, "*Delirium following mechanical thrombectomy for ischemic stroke – individuals at risk, imaging biomarkers and prognosis*", 747 patients who underwent mechanical thrombectomy for large vessel occlusion stroke had an 8.2% incidence of delirium, resulting in worse functional outcomes at 90 days. Key risk factors identified included age, sex, anesthesia, infections, stroke etiologies, and medial temporal lobe atrophy scores (Hahn et al.).

In conclusion, addressing delirium in older adults requires a proactive, multidisciplinary approach. Strategies like reducing medications, monitoring biomarkers, and using assessment tools aim to minimize delirium's occurrence and impact. Focusing on personalized care can further reduce delirium risk, improving outcomes and quality of life for elderly patients. Integrating these findings into clinical practice can help reduce the burden of delirium and enhance recovery.

Author contributions

PM: Writing – review & editing. KH: Writing – original draft, Writing – review & editing.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Anticholinergic Drug Exposure Increases the Risk of Delirium in Older Patients Undergoing Elective Surgery

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Introduction: Postoperative delirium (POD) is a common and serious adverse event of surgery in older people. Because of its great impact on patients' safety and quality of life, identification of modifiable risk factors could be useful. Although preoperative medication intake is assumed to be an important modifiable risk factor, the impact of anticholinergic drugs on the occurrence of POD seems underestimated in elective surgery. The aim of this study was to investigate the association between preoperative anticholinergic burden and POD. We hypothesized that a high preoperative anticholinergic burden is an independent, potentially modifiable predisposing and precipitating factor of POD in older people.

Methods: Between November 2017 and April 2019, 1,470 patients of 70 years and older undergoing elective orthopedic, general, cardiac, or vascular surgery were recruited in the randomized, prospective, multicenter PAWEL trial. Anticholinergic burden of a sub-cohort of 899 patients, who did not receive a multimodal intervention for preventing POD, was assessed by two different tools at hospital admission: The established Anticholinergic Risk Scale (ARS) and the recently developed Anticholinergic Burden Score (ABS). POD was detected by confusion assessment method (CAM) and a validated post discharge medical record review. Logistic regression analyses were performed to evaluate the association between anticholinergic burden and POD.

Results: POD was observed in 210 of 899 patients (23.4%). Both ARS and ABS were independently associated with POD. The association persisted after adjustment for relevant confounding factors such as age, sex, comorbidities, preoperative cognitive and physical status, number of prescribed drugs, surgery time, type of surgery and anesthesia, usage of heart-lung-machine, and treatment in intensive care unit. If a patient

was taking one of the 56 drugs listed in the ABS, risk for POD was 2.7-fold higher (OR = 2.74, 95% CI = 1.55–4.94) and 1.5-fold higher per additional point on the ARS (OR = 1.54, 95% CI = 1.15–2.02).

Conclusion: Preoperative anticholinergic drug exposure measured by ARS or ABS was independently associated with POD in older patients undergoing elective surgery. Therefore, identification, discontinuation or substitution of anticholinergic medication prior to surgery may be a promising approach to reduce the risk of POD in older patients.

Keywords: delirium, acute encephalopathy, surgery, anticholinergic, geriatric, postoperative

INTRODUCTION

Delirium is a neuropsychiatric syndrome defined by acute decline and fluctuation of attention, cognitive function, and disturbance of awareness (1). Especially in older patients, delirium is a common and serious adverse event of surgery (2) with an incidence ranging from 11 to 51% (3, 4). Postoperative delirium (POD) in older people is often associated with persistent cognitive dysfunction, dementia, higher rates of institutionalization, and increased morbidity and mortality (5, 6). Its etiology is believed to be multifactorial. Besides neuro-inflammation and blood-brain barrier leakage, a neurotransmitter disbalance in terms of acetylcholine deficiency and dopamine excess is thought to be involved in the pathogenesis of delirium (7). Electroencephalographic changes in delirium such as occipital slowing are also indicative of acetylcholine deficiency (8). Multiple pre- and perioperative risk factors are known to predispose to delirium. Preoperative factors comprise age, multimorbidity, frailty, polypharmacy, and deficits in cognitive, sensory, and mobility function (9, 10). Perioperative parameters that have been identified are, for example, type of surgery and anesthesia, surgery time and treatment in intensive care units (2, 9). Because delirium negatively affects patients' safety and quality of life, identifying modifiable risk factors could be of great relevance for its prevention, especially in older patients (11–13). In this regard, preoperative medication use is considered one of the most important potentially modifiable factors in the prevention of POD (14).

Assuming that delirium might be precipitated by an imbalance in cerebral neurotransmission specifically including acetylcholine deficiency (15), drugs with anticholinergic properties (DAPs) could have a significant impact on POD. DAPs are frequently prescribed in older people for a variety of indications such as minor and major depression, bladder disorders, or nausea (16). The cumulative effect of all DAPs taken regularly by an individual is often referred to as the anticholinergic burden (17). However, numerous studies indicated adverse effects of DAPs on cognitive and physical function (18, 19). Anticholinergic burden has been associated with delirium in several settings (18, 20, 21), although results were conflicting (22). Studies on the effect of DAPs on POD are less frequent, and their results were also inconsistent, with one positive (23) and two negatives studies (24, 25). Different results could be caused by the use of different scores calculating anticholinergic burden, small sample sizes, and different definitions of delirium. Therefore, in this study, we used the established Anticholinergic Risk Scale (ARS), which was most consistently associated with delirium (22). In addition, we applied a new, promising score developed in a very large sample of 250,000 participants to assess associations between long-term anticholinergic medication use and the risk of dementia (16). We hypothesized that a high preoperative anticholinergic burden is an independent, potentially modifiable predisposing and precipitating factor for POD in older people.

METHODS

Study Design

This study is based on a secondary analysis of data collected from 1,470 patients between November 2017 and April 2019 for the PAWEL-Study (Patient safety, cost-effectiveness and quality of life: reduction of delirium risk and postoperative cognitive dysfunction after elective procedures in older adults). The complete protocol for this randomized, prospective, multicenter study has been described in detail previously (12). Briefly, inclusion criteria comprised patients aged 70 years and older scheduled for elective surgery with an expected duration of surgery of at least 60 min. Surgical procedures included orthopedic, general, cardiac, and vascular surgery conducted at five medical centers in the southwest of Germany. Exclusion criteria were life expectancy <15 months, insufficient knowledge of German language, and recently diagnosed severe dementia without a legal representative. We included the sub-cohort of 899 participants of the baseline group who did not receive a multimodal intervention for preventing POD analogous to the PAWEL risk factor study (10).

Data Collection in the Pre-, Peri-, and Postoperative Phase

Demographic and clinical data were collected at baseline, no more than 3 weeks before the scheduled surgery, including medical history by Charlson Comorbidity Index (26), cognitive screening by Montreal Cognitive Assessment [MoCA, (27)], preoperative physical status by classification of the American Society of Anesthesiologists [ASA, (28)], and functional status by Barthel Index (29) as well as nutritional condition by Body Mass Index. Preoperative depression and anxiety symptoms were assessed by the Patient Health Questionnaire (30).

Perioperative data included premedication, surgical procedure with or without cardiopulmonary bypass, cut-to-suture time, and type of anesthesia. Parameters were collected from anesthesia and surgery protocols.

Anticholinergic Drug Exposure

Each patient's medication was analyzed on admission using the medication list and personal medical history. Long-term medications as well as "as-needed" ("PRN") medication were included in the analysis if they were taken more than 3 days a week. In view of the high proportion of "over-the-counter"-drugs, the use of sleeping pills was explicitly queried. Preoperative anticholinergic burden was calculated for each patient using the Anticholinergic Risk Scale [ARS (31)]. Briefly summarized, the ARS is a weighted score developed by Rudolph et al. (31), which often has been used in studies investigating the association between anticholinergic burden and delirium in different study populations (21). It comprises 49 DAPs evaluated from 0 (no or low anticholinergic activity) to 3 (highest anticholinergic activity). The sum of all values provides the patient's individual anticholinergic burden. However, the ARS has not been updated since 2008 and the weights of different DAPs are a matter of debate (22). We therefore added the anticholinergic score recently published by Coupland et al. (16). This measure is primarily based on the score of Gray et al. (32) which comprises medications with strong anticholinergic properties identified by the American Geriatrics Society Beers Criteria Update Expert panel (33). Originally, this anticholinergic score was intended to assess the cumulative anticholinergic burden to evaluate associations between long-term anticholinergic drug exposure and the risk of dementia in a large cohort (16). Hereinafter, this score is called Anticholinergic Burden Score (ABS). The ABS includes 56 DAPs of different subgroups which previously have been described in detail (16). In contrast to the ARS, the ABS does not weigh anticholinergic properties of medications but counts the number of received DAPs. Therefore, in this study, we define the preoperative anticholinergic burden as the sum of all DAPs according to the ABS. We did not include the cumulative dosage of the identified DAPs. To our best knowledge, the ABS is used to investigate the association between anticholinergic burden and POD here for the first time.

Outcome Measures

Primary outcome measure was the occurrence of POD after elective surgery. POD was evaluated daily for up to 7 postoperative days by independent and previously trained assessors (10, 12) using the Confusion Assessment Method in a German operationalized version [CAM, (34, 35)]. Additionally, a chart review based on the DSM-V criteria for delirium (1) was conducted by experienced physicians at discharge. Similar to the SAGES Study (36), POD was defined if at least one of the methods indicated delirium (37).

Statistical Analysis

Differences between patients with and without POD were evaluated for categorical variables by χ^2 test and for non-normally distributed continuous variables by Mann-Whitney *U* test. Logistic regression analysis was used to investigate the independent association of preoperative anticholinergic burden and the incidence of POD (Odds Ratios with 95% confidence intervals). First, univariate logistic regression was performed for both, ARS and ABS. In a second step, the model was adjusted for items that were found to be strong confounders in previous studies (2, 4, 10). These were age, sex, Charlson Comorbidity Index, preoperative cognitive status (MoCA), physical status (ASA), number of prescribed drugs, preoperative serum creatinine, surgery time, type of surgery and anesthesia, usage of heart-lung-machine, and treatment in intensive care unit. Missing data in confounding variables led to the exclusion of 53 patients from the adjusted multivariate analysis, which was finally performed on 846 patients. Data were analyzed with the software IBM SPSS Statistics Version 25 (IBM Corporation, Armonk, NY, USA). Results were considered statistically significant at a level of $p < 0.05$.

RESULTS

Participants' Characteristics

The sociodemographic and clinical characteristics of all 899 patients aged 70 and older are described in **Table 1**. The mean age of the participants was 77.3 years (range 70–98 years), and 49.4% were female. According to the Charlson Comorbidity Index, 282 patients (31.4%) had at least three diseases. Participants were taking a median of six drugs with 56.6% taking ≥5 drugs. Most of the enrolled patients had orthopedic surgery (e.g., hip, knee, and spine, $n = 474$, 52.7%). Another group of 377 patients (37.5%) received cardiovascular interventions with or without cardiopulmonary bypass. The remaining 88 patients (9.8%) underwent general surgery (e.g., abdominal surgery). Surgeries were mostly performed under general anesthesia ($n = 726$, 80.8%).

POD was observed in 210 (23.4%) patients. Patients diagnosed with POD took significantly more medications ($p < 0.001$), had more comorbidities ($p = 0.004$), and revealed a lower MoCA level at baseline assessment ($p < 0.001$). Furthermore, patients with POD had a longer surgery time ($p < 0.001$), and were admitted to an intensive care unit more often ($p < 0.001$). POD occurred significantly more often in patients requiring cardiopulmonary bypass ($p < 0.001$). General anesthesia was performed more frequently in patients with POD ($p = 0.023$). POD and non-POD groups did not differ statistically in Body Mass Index, educational level, Barthel Index, preoperative depression, anxiety or treatment with benzodiazepines (see **Table 1**).

Association Between Preoperative Anticholinergic Burden and POD

Using the ARS score, 81 patients (9%) were taking at least one anticholinergic drug. Patients with POD had a significantly higher ARS value than patients without POD ($p = 0.004$). Evaluating medication according to ABS criteria, 71 patients (8%) were taking DAPs. Comparing the POD and non-POD groups, the rate of DAPs was significantly higher in patients with POD (ABS = 1: 6 vs. 11%, ABS = 2: 0 vs. 7%). The most frequently prescribed DAP in both groups (according the ABS

TABLE 1 | Sociodemographic and clinical characteristics of enrolled patients.

	Overall sample	No POD $n = 689$ (76.6%)	POD $n = 210$ (23.4%)	*p*
Age, in years, mean (SD)				
n = 899	77.3 (4.9)	77.2 (4.8)	77.8 (5.2)	0.153
Female sex, *n* (%)				
n = 899	444 (49.4)	353 (51.2)	91 (43.3)	**0.045**
Education in years, mean (SD)				
n = 882	12.2 (3.0)	12.3 (3.0)	12.2 (2.9)	0.375
MoCA, mean (SD)				
n = 874	23.4 (3.9)	23.9 (3.4)	21.7 (4.8)	**<0.001**
Charlson Comorbidity Index, median (IQR)				
n = 899	2.0 (0.0–3.0)	2.0 (0.0–3.0)	2.0 (1.0 - 3.0)	**0.004**
Barthel index, *n* (%)				
= 100	596 (68.0)	464 (68.6)	132 (65.7)	0.368
= 85–95	183 (20.9)	142 (21.0)	41 (20.4)	
<85	98 (11.1)	70 (10.4)	28 (13.9)	
n = 877				
Number of preoperative medications, median (IQR)				
n = 899	6.0 (4.0–9.0)	6.0 (4.0–8.0)	7.0 (5.0–9.0)	**<0.001**
PHQ-4, median (IQR)				
n = 870	1.0 (0–3)	1.0 (0–6)	1.0 (0–6)	0.568
Preoperative benzodiazepines, *n* (%)				
n = 894	237 (26.4)	174 (25.4)	63 (30.1)	0.174
Preoperative creatinine in mg/l, median (IQR)				
n = 881	0.9 (0.8–1.1)	0.9 (0.7–1.1)	0.9 (0.8–1.2)	**0.014**
BMI in kg/m^2, median (IQR)				
n = 885	26.64 (24.09–29.81)	26.66 (24.03–29.93)	26.64 (24.22–29.73)	0.861
ASA classification, *n* (%)				
ASA 1 + 2	246 (27.7)	227 (33.4)	19 (9.2)	**<0.001**
ASA 3 + 4	641 (72.3)	453 (66.6)	188 (90.8)	
n = 887				
Surgery type, % orthopedic				
Cardiovascular	474 (52.7)	400 (58.1)	74 (35.2)	**<0.001**
Visceral/general	337 (37.5)	216 (31.3)	121 (57.6)	
n = 899	88 (9.8)	73 (10.6)	15 (7.2)	
Surgery time in min., mean (SD)				
n = 898	146.6 (84.7)	133.1 (74.5)	191.1 (100.0)	**<0.001**
General anesthesia, *n* (%)				
n = 892	726 (80.8)	545 (79.1)	181 (86.2)	**0.023**
Stay at ICU/IMC, *n* (%)				
n = 893	538 (60.2)	368 (53.8)	170 (81.3)	**<0.001**
Cardiopulmonary bypass, *n* (%)				
n = 894	243 (27.2)	147 (21.5)	96 (45.9)	**<0.001**

SD, standard deviation; IQR, interquartile range; MoCA, Montreal Cognitive Assessment; ICU, Intensive Care Unit; IMC, Intermediate Care Unit; BMI, Body Mass Index; ASA, American Society of Anesthesiologists; PHQ-4, Patient Health Questionnaire. Significant p-values are marked in bold.

criteria) was amitriptyline ($n = 8$ in each group) followed in the delirium group by doxepine ($n = 4$) and solifenacin ($n = 3$). In patients without POD, trospium ($n = 7$) and trimipramine ($n = 6$) were the most commonly used DAPs, in addition to amitriptyline. The top 10 DAPs prescribed are shown in **Figure 1**.

Although the number of patients taking DAPs and the number of different DAPs (ARS: $n = 22$, ABS: $n = 19$) was relatively small in our study population, we found significant group differences. This was the case when ARS was used and when ABS criteria were applied. In the subgroup of 71 patients who received one or two ABS drugs, the POD rate was 42.3% ($n = 30/71$) and thus almost

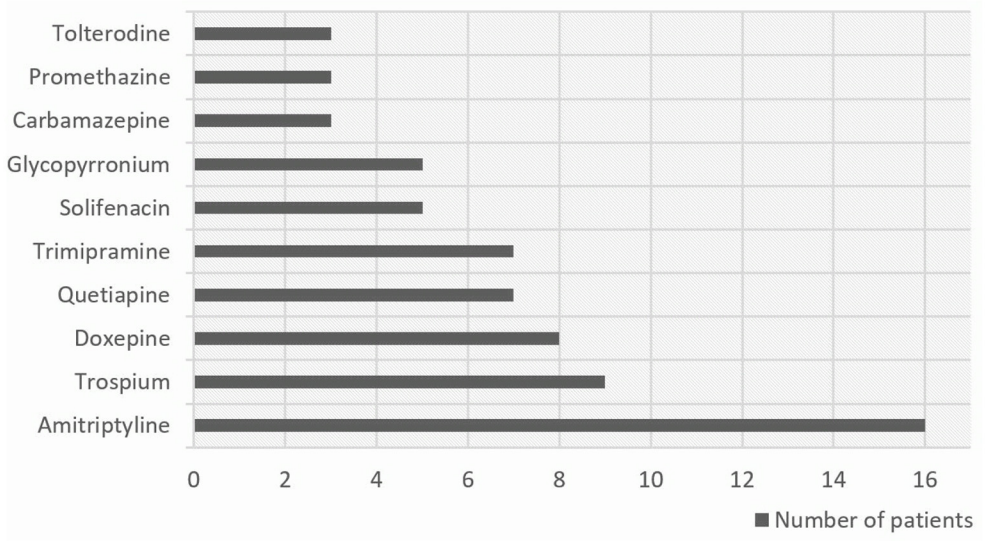

FIGURE 1 | The ten most prescribed DAPs in our study population according to the Anticholinergic Burden Score (ABS).

TABLE 2 | Characteristics of anticholinergic burden according to ARS and ABS in patients with and without postoperative delirium.

	Overall sample ***n* = 899**	**No POD** ***n* = 689 (76.6%)**	**POD** ***n* = 210 (23.4%)**	***p***
ARS, mean ± SD (range)	0.17 ± 0.63 (0–5)	0.13 ± 0.50 (0–3)	0.32 ± 0.93 (0–5)	**0.004**
No AB (ARS = 0), *n* (%)	818 (91.0)	637 (92.5)	181 (86.2)	**<0.001**
Moderate AB (ARS = 1), *n* (%)	38 (4.2)	26 (3.8)	12 (5.7)	
Strong AB (ARS = 2), *n* (%)	19 (2.1)	16 (2.3)	3 (1.4)	
High AB (ARS ≥ 3), *n* (%)	24 (2.7)	10 (1.4)	14 (6.7)	
ABS = 0	828 (92.1)	648 (94)	180 (85.7)	**<0.001**
ABS = 1	64 (7.1)	41 (6.0)	23 (11.0)	
ABS = 2	7 (0.8)	0 (0,0)	7 (3.3)	

SD, standard deviation; IQR, interquartile range; ARS, Anticholinergic Risk Scale; AB, anticholinergic burden; ABS, Anticholinergic Burden Score. Significant p-values are marked in bold.

twice as high as in the group without ABS medication where POD occurred in only 21.7% ($n = 180/828$, see **Table 2**).

Univariate logistic regression analysis revealed a positive association with the occurrence of POD for both scales, ARS and ABS. Odds ratios (ORs) and corresponding 95% confidence intervals (CI) are provided in **Table 3**. After adjustment for confounding variables, ORs changed only marginally and the positive association with the occurrence of POD persisted. Each additional point in the ARS was associated with a 1.5-fold higher risk of developing POD (OR = 1.54, 95% CI = 1.15–2.02). Applying the ABS criteria resulted in a 2.7 higher likelihood of POD (OR = 2.74, 95% CI = 1.55–4.94) for each additional DAP.

One of the confounding variables we included in the adjusted regression analysis (**Table 3**) was the ASA physical status classification, which is widely used to assess pre-anesthesia medical comorbidities. The Barthel Index is commonly applied to assess the functional status of older patients. Thus, we additionally performed an adjusted regression analysis using the Barthel Index instead of the ASA classification. The ORs for both, ARS (OR = 1.37, 95% CI = 1.04–1.81) and ABS (OR = 2.44, 95% CI = 1.39–4.28), changed only slightly. This result confirms that neither physical status (ASA) nor functional status (Barthel Index) accounted for the increase of POD with anticholinergic medication.

DISCUSSION

Preoperative anticholinergic medication exposure was assessed by two different scales estimating the overall anticholinergic burden, the weighted ARS and the more recent ABS. The findings of this study suggest that anticholinergic medication usage might be an independent risk factor for POD in older population undergoing elective surgery. The reduction or omission of these drugs preoperatively might thus be beneficial for the prevention of POD.

Our results are in line with several previous studies, which reported an association between anticholinergic drug exposure

measured with the ARS and the occurrence of delirium in older patients (38–41). A recently published systematic review by Egberts et al. showed that among the variety of existing anticholinergic drug scales, the Anticholinergic Risk Scale (ARS) was the only one found to be consistently associated with delirium (22). Also, our findings are in accordance with a published study by Mueller et al. who showed an independent association between preoperative anticholinergic burden and the occurrence of POD (prevalence 10%) in a sample of older cancer patients (mean age 71 years, $n = 651$) (23). Yet, in contrast to our study, this study used the Anticholinergic Drug Score (42) to determine the anticholinergic burden. Other studies did not find an association between anticholinergic burden and delirium (43, 44). Reasons for the inconsistent results of the studies are manifold. One reason could be that the measurement of the anticholinergic load has not yet been standardized (22). This leads to a large body of existing literature concerning DAPs and a lack of consensus on how to quantify the anticholinergic burden. In recent years, numerous different scales have been developed. However, they vary widely in their structure, focus, application, measurement of anticholinergic properties (serum vs. predefined) and association with outcomes (21). Therefore, comparability of individual study findings is limited, and an international consent on the most feasible instrument is strongly needed. The use of different tools to determine the anticholinergic burden is one explanation for the inconsistent findings of previous studies. Furthermore, there is a large heterogeneity in study populations comprising residents of nursing homes (38), Australian veterans (45), Taiwanese National Health Insurance database (46), palliative care inpatients (39) and acutely ill hospitalized patients (20, 40), making it even more difficult to compare results. Moorey et al. claimed that delirium is not associated with the anticholinergic burden in older patients on admission to an acute hospital (43). In contrast to our study, they used the Anticholinergic Cognitive Burden Scale (47) and the Anticholinergic Drug Score which were both not consistently associated with delirium (22). Pasina et al. also used the Anticholinergic Cognitive Burden Scale in their recently published study and did not find a clear association between anticholinergic burden and delirium in patients admitted to an acute geriatric ward (44). Also, in contrast to our findings, a recently published study by Heinrich et al. found no association between preoperative anticholinergic load and POD using the Anticholinergic Cognitive Burden Scale, the Anticholinergic Drug Score and the ARS (24). However, compared to our study, these patients were significantly younger (POD: 74 years, no POD: 71 years in median) and patients with more than mild cognitive impairment (Mini-Mental State Examination score $\leq$ 23 points) were excluded.

As mentioned above, to our best knowledge, this is the first study using the ABS to explore the effect of DAPs on delirium. In comparison to the ARS, ORs for occurrence of POD were clearly higher using the ABS than the ARS. Our results suggest a 2.7-fold risk of developing a POD for each drug included in the ABS. Therefore, our findings provide a strong argument for modifiable delirium risk assessment by ABS in older patients scheduled for surgery. The PAWEL study's intervention bundle AKTIVER (Alltags- und Kognitions-Training & Interdisziplinarität verbessert Ergebnis und mindert das Risiko ["everyday skills and cognition training and interdisciplinarity improves outcome and mitigates risk"]) has been shown to reduce delirium by 33% in patients undergoing elective orthopedic and abdominal surgery by daily application of individualized modules on activation, relaxation and diagnostic chaperonage during the hospital stay (37). In addition to those actions for delirium prevention, software programs, or an app could be implemented into the hospital clinical information system to raise awareness of detrimental drugs even before surgery of older patients to enable discontinuation or substitution prior to anesthesia to avoid postoperative delirium. In most cases, alternatives more appropriate for older people are available or medication is not crucial during the vulnerable perioperative period. However, further studies are required to validate ABS as a useful tool to reduce the risk of POD in older patients in addition to the AKTIVER bundle.

TABLE 3 | Odds ratios for postoperative delirium according to ARS and ABS.

	Model 1: Univariate model		Model 2: Adjusted model	
Variable	**OR (95% CI)**	***p***	**OR (95% CI)**	***p***
ARS	1.49 (1.21–1.85)	**<0.001**	1.54 (1.15–2.02)	**0.002**
ABS	2.76 (1.77–4.30)	**<0.001**	2.74 (1.55–4.94)	**0.001**

OR, odds ratio; using no anticholinergic burden as reference. CI, confidence interval; ARS, Anticholinergic Risk Scale; ABS, Anticholinergic Burden Score.
Model 2 was adjusted for age, sex, preoperative cognitive status, number of drugs, Charlson Comorbidity Index, ASA classification, type of surgery, use of cardiopulmonary bypass, general anesthesia yes/no, cut-to-suture-time, IMC/ICU stay, and preoperative creatinine. Significant p-values are marked in bold.

LIMITATIONS AND STRENGTHS

This study has several limitations. First, our approach to measure anticholinergic drug exposure did not include the dosages of DAPs. It is quite conceivable that higher dosages of DAPs have a stronger negative impact on the development of POD. Second, the ARS was developed in 2008 and was not updated since then. This could lead to an underestimation of anticholinergic burden due to an abandonment of newer DAPs. Third, we collected our information from patients' medication lists and verbal information but had little information about adherence to prescriptions prior to hospital admission. Finally, we did not consider delirium severity and duration in this study. The strengths of our study are the prospective multicenter study-design, the large number of patients and the usage of two different tools to measure anticholinergic burden. In addition to the established ARS as a weighted score, we used ABS as a quick and simple instrument to quantify anticholinergic burden in delirium patients for the first time. A further strength is the relatively high number of strong confounders like cognition included in our multivariable regression analysis.

CONCLUSION

This study of 899 older patients undergoing various elective surgical procedures shows that the preoperative anticholinergic

burden, assessed by ARS or ABS, is an independent risk factor for POD in older patients. Delirium occurrence was more than 2.7 times higher if a patient took at least one of the 56 drugs listed in the ABS (16), even after controlling for the most known delirium risk factors. The POD rate increased from 21.7 to 42.3% in patients receiving one or two ABS drugs. Identifying DAPs prior to hospital admission might be an opportunity to terminate or substitute anticholinergic drugs preoperatively and prevent delirium after elective surgery.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was approved by the Ethics Commission of the Faculty of Medicine of the Eberhard-Karls University and University Hospital Tübingen with number 233/2017BO1 on October 12, 2017 and by the Ethics Commission of the University of Potsdam with number 38/2017 on December 11, 2017. The study was registered on the German Clinical Trials Register (DRKS-ID: DRKS00012797) in July, 2017. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MH, CT, and GE designed this secondary analysis of the PAWEL-Study, planned the data collection, performed the statistical analysis, and prepared and revised the manuscript. CB, CM, FK, EM, SW, LC, BF, MR, CA, and MD were involved in data collection and critically revised the manuscript for final approval of the version to be published. All authors contributed to the article and approved the submitted version.

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REFERENCES

1. American Psychiatric, A.ssociation. *Diagnostic and Statistical Manual of Mental Disorders (5th Edn)*. (2013). doi: 10.1176/appi.books.9780890425596
2. Aldecoa C, Bettelli G, Bilotta F, Sanders RD, Audisio R, Borozdina A, et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. *Eur J Anaesthesiol.* (2017) 34:192–214. doi: 10.1097/EJA.0000000000000594
3. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet.* (2014) 383:911–22. doi: 10.1016/S0140-6736(13)60688-1
4. American Geriatrics Society. American Geriatrics Society abstracted clinical practice guideline for postoperative delirium in older adults. *J Am Geriatr Soc.* (2015) 63:142–50. doi: 10.1111/jgs.13281
5. Ansaloni L, Catena F, Chattat R, Fortuna D, Franceschi C, Mascitti P, et al. Risk factors and incidence of postoperative delirium in elderly patients after elective and emergency surgery. *Br J Surg.* (2010) 97:273–80. doi: 10.1002/bjs.6843
6. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA.* (2010) 304:443–51. doi: 10.1001/jama.2010.1013
7. Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. *Am J Geriatr Psychiatry.* (2013) 21:1190–222. doi: 10.1016/j.jagp.2013.09.005
8. Thomas C, Hestermann U, Kopitz J, Plaschke K, Oster P, Driessen M, et al. Serum anticholinergic activity and cerebral cholinergic dysfunction: an EEG study in frail elderly with and without delirium. *BMC Neurosci.* (2008) 9:86. doi: 10.1186/1471-2202-9-86
9. Guenther U, Riedel L, Radtke FM. Patients prone for postoperative delirium: preoperative assessment, perioperative prophylaxis, postoperative treatment. *Curr Opin Anaesthesiol.* (2016) 29:384–90. doi: 10.1097/ACO.0000000000000327
10. Eschweiler GW, Czornik M, Herrmann ML, Knauer YP, Forkavets O, von Arnim CAF, et al. Presurgical screening improves risk prediction for delirium in elective surgery of older patients: the PAWEL RISK study. *Front Aging Neurosci.* (2021) 13:679933. doi: 10.3389/fnagi.2021.679933
11. Martinez F, Tobar C, Hill N. Preventing delirium: should non-pharmacological, multicomponent interventions be used? A systematic review and meta-analysis of the literature. *Age Ageing.* (2015) 44:196–204. doi: 10.1093/ageing/afu173
12. Sanchez A, Thomas C, Deeken F, Wagner S, Kloppel S, Kentischer F, et al. Patient safety, cost-effectiveness, and quality of life: reduction of delirium risk and postoperative cognitive dysfunction after elective procedures in older adults-study protocol for a stepped-wedge cluster randomized trial (PAWEL Study). *Trials.* (2019) 20:71. doi: 10.1186/s13063-018-3148-8
13. Burton JK, Craig LE, Yong SQ, Siddiqi N, Teale EA, Woodhouse R, et al. Non-pharmacological interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database Syst Rev.* (2021) 7:Cd013307. doi: 10.1002/14651858.CD013307.pub2
14. Kassie GM, Nguyen TA, Kalisch Ellett LM, Pratt NL, Roughead EE. Preoperative medication use and postoperative delirium: a systematic review. *BMC Geriatr.* (2017) 17:298. doi: 10.1186/s12877-017-0695-x
15. Collamati A, Martone AM, Poscia A, Brandi V, Celi M, Marzetti E, et al. Anticholinergic drugs and negative outcomes in the older population: from biological plausibility to clinical evidence. *Aging Clin Exp Res.* (2016) 28:25–35. doi: 10.1007/s40520-015-0359-7
16. Coupland CAC, Hill T, Dening T, Morriss R, Moore M, Hippisley-Cox J. Anticholinergic drug exposure and the risk of dementia: a nested case-control study. *JAMA Intern Med.* (2019) 179:1084–93. doi: 10.1001/jamainternmed.2019.0677
17. Tune LE. Anticholinergic effects of medication in elderly patients. *J Clin Psychiatry.* (2001) 62:11–4. Available online at: https://www.psychiatrist.com/read-pdf/833/

18. Fox C, Smith T, Maidment I, Chan WY, Bua N, Myint PK, et al. Effect of medications with anti-cholinergic properties on cognitive function, delirium, physical function and mortality: a systematic review. *Age Ageing.* (2014) 43:604–15. doi: 10.1093/ageing/afu096
19. Salahudeen MS, Duffull SB, Nishtala PS. Anticholinergic burden quantified by anticholinergic risk scales and adverse outcomes in older people: a systematic review. *BMC Geriatr.* (2015) 15:31. doi: 10.1186/s12877-015-0029-9
20. Egberts A, van der Craats ST, van Wijk MD, Alkilabe S, van den Bemt P, Mattace-Raso FUS. Anticholinergic drug exposure is associated with delirium and postdischarge institutionalization in acutely ill hospitalized older patients. *Pharmacol Res Perspect.* (2017) 5:e00310. doi: 10.1002/prp2.310
21. Welsh TJ, van der Wardt V, Ojo G, Gordon AL, Gladman JRF. Anticholinergic drug burden tools/scales and adverse outcomes in different clinical settings: a systematic review of reviews. *Drugs Aging.* (2018) 35:523–38. doi: 10.1007/s40266-018-0549-z
22. Egberts A, Moreno-Gonzalez R, Alan H, Ziere G, Mattace-Raso FUS. Anticholinergic drug burden and delirium: a systematic review. *J Am Med Dir Assoc.* (2021) 22:65–73.e64. doi: 10.1016/j.jamda.2020.04.019
23. Mueller A, Spies CD, Eckardt R, Weiss B, Pohrt A, Wernecke KD, et al. Anticholinergic burden of long-term medication is an independent risk factor for the development of postoperative delirium: a clinical trial. *J Clin Anesth.* (2019) 61:109632. doi: 10.1016/j.jclinane.2019.109632
24. Heinrich M, Muller A, Cvijan A, Morgeli R, Kruppa J, Winterer G, et al. Preoperative comparison of three anticholinergic drug scales in older adult patients and development of postoperative delirium: a prospective observational study. *Drugs Aging.* (2021) 38:347–54. doi: 10.1007/s40266-021-00839-5
25. Tillemans MPH, Butterhoff-Terlingen MH, Stuffken R, Vreeswijk R, Egberts TCG, Kalisvaart KJ. The effect of the anticholinergic burden on duration and severity of delirium in older hip-surgery patients with and without haloperidol prophylaxis: a *post hoc* analysis. *Brain Behav.* (2021) 11:e2404. doi: 10.1002/brb3.2404
26. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* (1987) 40:373–83. doi: 10.1016/0021-9681(87)90171-8
27. Nasreddine ZS, Phillips NA, Bedirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc.* (2005) 53:695–9. doi: 10.1111/j.1532-5415.2005.53221.x
28. Wolters U, Wolf T, Stutzer H, Schroder T. ASA classification and perioperative variables as predictors of postoperative outcome. *Br J Anaesth.* (1996) 77:217–22. doi: 10.1093/bja/77.2.217
29. Lubke N, Meinck M, Von Renteln-Kruse W. [The Barthel Index in geriatrics. A context analysis for the Hamburg Classification Manual]. *Z Gerontol Geriatr.* (2004) 37:316–26. doi: 10.1007/s00391-004-0233-2
30. Kroenke K, Spitzer RL, Williams JB, Lowe B. An ultra-brief screening scale for anxiety and depression: the PHQ-4. *Psychosomatics.* (2009) 50:613–21. doi: 10.1176/appi.psy.50.6.613
31. Rudolph JL, Salow MJ, Angelini MC, McGlinchey RE. The anticholinergic risk scale and anticholinergic adverse effects in older persons. *Arch Intern Med.* (2008) 168:508–13. doi: 10.1001/archinternmed.2007.106
32. Gray SL, Anderson ML, Dublin S, Hanlon JT, Hubbard R, Walker R, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med.* (2015) 175:401–7. doi: 10.1001/jamainternmed.2014.7663
33. American Geriatrics Society. American Geriatrics Society 2019 Updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. *J Am Geriatr Soc.* (2019) 67: 674–94. doi: 10.1111/jgs.15767
34. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med.* (1990) 113:941–8. doi: 10.7326/0003-4819-113-12-941
35. Thomas C, Kreisel SH, Oster P, Driessen M, Arolt V, Inouye SK. Diagnosing delirium in older hospitalized adults with dementia: adapting the confusion assessment method to international classification of diseases, tenth revision, diagnostic criteria. *J Am Geriatr Soc.* (2012) 60:1471–7. doi: 10.1111/j.1532-5415.2012.04066.x
36. Schmitt EM, Saczynski JS, Kosar CM, Jones RN, Alsop DC, Fong TG, et al. The Successful Aging after Elective Surgery (SAGES) study: cohort description and data quality procedures. *J Am Geriatr Soc.* (2015) 63:2463–71. doi: 10.1111/jgs.13793
37. Deeken F, Sanchez A, Rapp MA, Denkinger M, Brefka S, Spank J, et al. Outcomes of a delirium prevention program in older persons after elective surgery: a stepped-wedge cluster randomized clinical trial. *JAMA Surg.* (2021) 157:e216370. doi: 10.1001/jamasurg.2021.6370
38. Landi F, Dell'Aquila G, Collamati A, Martone AM, Zuliani G, Gasperini B, et al. Anticholinergic drug use and negative outcomes among the frail elderly population living in a nursing home. *J Am Med Dir Assoc.* (2014) 15:825–9. doi: 10.1016/j.jamda.2014.08.002
39. Zimmerman KM, Salow M, Skarf LM, Kostas T, Paquin A, Simone MJ, et al. Increasing anticholinergic burden and delirium in palliative care inpatients. *Palliat Med.* (2014) 28:335–41. doi: 10.1177/0269216314522105
40. Wolters AE, Zaal IJ, Veldhuijzen DS, Cremer OL, Devlin JW, van Dijk D, et al. Anticholinergic medication use and transition to delirium in critically ill patients: a prospective cohort study. *Crit Care Med.* (2015) 43:1846–52. doi: 10.1097/CCM.0000000000001094
41. Hwang S, Jun K, Ah YM, Han E, Chung JE, Lee JY. Impact of anticholinergic burden on emergency department visits among older adults in Korea: a national population cohort study. *Arch Gerontol Geriatr.* (2019) 85:103912. doi: 10.1016/j.archger.2019.103912
42. Carnahan RM, Lund BC, Perry PJ, Pollock BG, Culp KR. The Anticholinergic Drug Scale as a measure of drug-related anticholinergic burden: associations with serum anticholinergic activity. *J Clin Pharmacol.* (2006) 46:1481–6. doi: 10.1177/0091270006292126
43. Moorey HC, Zaidman S, Jackson TA. Delirium is not associated with anticholinergic burden or polypharmacy in older patients on admission to an acute hospital: an observational case control study. *BMC Geriatr.* (2016) 16:162. doi: 10.1186/s12877-016-0336-9
44. Pasina L, Colzani L, Cortesi L, Tettamanti M, Zambon A, Nobili A, et al. Relation between delirium and anticholinergic drug burden in a cohort of hospitalized older patients: an observational study. *Drugs Aging.* (2019) 36:85–91. doi: 10.1007/s40266-018-0612-9
45. Kalisch Ellett LM, Pratt NL, Ramsay EN, Barratt JD, Roughead EE. Multiple anticholinergic medication use and risk of hospital admission for confusion or dementia. *J Am Geriatr Soc.* (2014) 62:1916–22. doi: 10.1111/jgs.13054
46. Huang KH, Chan YF, Shih HC, Lee CY. Relationship between Potentially Inappropriate Anticholinergic Drugs (PIADs) and adverse outcomes among elderly patients in Taiwan. *J Food Drug Anal.* (2012) 20:930–937+985. doi: 10.6227/jfda.2012200423
47. Boustani M, Campbell N, Munger S, Maidment I, Fox C. Impact of anticholinergics on the aging brain: a review and practical application. *Aging Health.* (2008) 4:311–20. doi: 10.2217/1745509X.4.3.311

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Preoperative plasma visfatin may have a dual effect on the occurrence of postoperative delirium

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Background: Visfatin is considered to be a "novel pro-inflammatory cytokine." Neuroinflammatory response is one of the important mechanisms of postoperative delirium (POD). The relationship between preoperative plasma visfatin and POD is unclear.

Objective: To investigate the relationship between preoperative plasma visfatin concentrations and POD (primary outcome) in older hip fracture patients and to explore whether it affects POD through inflammatory factors.

Materials and methods: This prospective cohort study enrolled 176 elderly patients who were scheduled for hip fracture surgery. Preoperative plasma was collected on the morning of surgery, and visfatin levels were measured. Interleukin (IL)-1 and IL-6 were measured using patients' plasma collected on the first day after surgery. We used the 3-min diagnostic interview for Confusion Assessment Method-defined delirium (3D-CAM) twice daily within the 2 days after surgery to assess whether POD had occurred. Restricted cubic splines and piecewise regression were used to explore the relationship between preoperative plasma visfatin concentrations and POD, and further mediation analysis was used to verify whether visfatin plays a role in POD through regulating inflammatory factors.

Results: The incidence of POD was 18.2%. A J-shaped association was observed between preoperative plasma visfatin levels and POD. The risk of POD decreased within the lower visfatin concentration range up to 37.87 ng/ml, with a hazard ratio of 0.59 per 5 ng/ml [odds ratio (OR) = 0.59, 95% confidence interval (CI) = 0.37–0.95], but the risk increased above this concentration (P for non-linearity < 0.001, with a hazard ratio of 1.116 per 10 ng/ml; OR = 1.10, 95% CI = 1.02–1.23). Mediation effect analysis showed that when the plasma visfatin concentration was higher than 37.87 ng/ml, the effect of visfatin on POD was mediated by IL-6 ($p < 0.01$). A significant indirect association with postoperative plasma IL-6 was observed between

preoperative plasma visfatin and POD (adjusted β = 0.1%; 95% CI = 4.8∼38.9%; $p < 0.01$).

Conclusion: Visfatin is the protective factor in POD when the preoperative plasma visfatin concentration is below 37.87 ng/ml, but when it exceeds 37.87 ng/ml, the visfatin concentration is a risk factor for POD, which is mediated by postoperative plasma IL-6. The results suggest that preoperative visfatin may have a dual effect on the POD occurrence.

Clinical trial registration: [www.ClinicalTrials.gov], identifier [ChiCTR2100052674].

KEYWORDS

hip fracture, visfatin, postoperative delirium, interleukin-6, mediation analysis

Introduction

Hip fracture is a main disease that threaten the health and quality of life in older adults, and its incidence increases with population aging. Epidemiological data showed that one in five women and one in ten men have hip fractures globally per year, and most of them need surgery (1). Older adults undergoing hip fracture surgery have high disability and mortality rates, which become a serious medical, economic, and social problem (2).

Postoperative delirium (POD) is a common complication after hip fracture surgery in older patients (3). It is mainly manifested by changes in the level of consciousness, cognitive dysfunction, decreased attention, and disturbance of the sleep-wake cycle. The incidence rate is approximately 4–61% (4), which is depending on the type of surgery. Although it can occur at any time during a patient's hospital stay, POD usually develops during the first few days after surgery. POD is associated with poor outcomes such as longer duration of hospitalization, increased mortality rates, and increased morbidity (5). Additionally, it can affect the recovery of physical function and the return to normal life after discharge from the hospital.

The mechanism of POD mainly includes five theories including the neuroinflammation theory (6). A lot of studies have shown that IL-1 and IL-6 levels in the peripheral circulation are related to POD occurrence (7, 8).

Visfatin is a multi-functional protein molecule that is present in many organs and tissues in the body including brain (such as cortex and hippocampus area) and lung (9). Visfatin can exert multiple insulin simulation effects, including enhanced glucose intake and increased triglyceride synthesis (10). Visfatin is also regarded as a new type of inflammatory cytokine. Studies have shown that visfatin can activate monocytes to produce inflammatory cytokines such as interleukin (IL)-1ß, IL-6, and tumor necrosis factor α (TNF-α) (11). Recently, some studies showed increased concentrations of blood visfatin were associated with cognitive impairment (12–14). Moreover, some evidences which suggest that decreased visfatin levels might lead to dementia and Alzheimer's disease (15, 16). However, some other studies appeared that visfatin played an important role in cognitive function. One study showed visfatin reduced hippocampal CA1 cell death and protects against memory loss and cognitive decline in male rats (17). Another study showed that mice lacking visfatin appearing hippocampal and cortical atrophy, astrogliosis, microgliosis, and abnormal CA1 dendritic morphology with altered intrahippocampal connectivity and abnormal behavior; including hyperactivity, some defects in motor skills and memory impairment (18). All these results above suggested that there may be a complex relationship between visfatin and cognitive function. Currently, the relationship between blood visfatin levels and POD is unclear. We suspected that there is also a complex link between visfatin and POD.

Therefore, we conducted this prospective cohort study to identify the correlation between preoperative plasma visfatin and POD and to further explore whether it can affect POD through inflammation factors.

Materials and methods

Patients and setting

This study was approved by the Beijing Jishuitan Hospital Medical Science Research Ethics Committee (JLKS202103-35) and was conducted in accordance with the principles of the Declaration of Helsinki. Cerebrospinal fluid (CSF) samples were obtained for the purpose of laboratory research. All methods were performed in accordance with relevant guidelines and regulations. Written informed consent was obtained, and this study was registered at the Chinese Clinical Trial Registry (ChiCTR2100052674). All participants were recruited from Beijing Jishuitan Hospital (Beijing, China) from November 2021 to April 2022. Eligible patients who were willing to

participate in the study met the entry criteria described below. The inclusion criteria were as follows: at least 65 years old; diagnosed with unilateral hip fracture; operation 48 h after admission; hospital admission for surgical treatment of hip fracture; and American Society of Anesthesiologists (ASA) physical status classification II to III. There were 468 patients recruited into this study (Figure 1). All patients received intravenous patient-controlled analgesia after surgery (Sufentanil 0.1 μg/kg, flurbiprofen axetil 200 mg, tropisetron hydrochloride 10 mg, and normal saline to a volume of 100 ml). The exclusion criteria were as follows: dementia; psychiatric patients; preoperative delirium; Parkinson's disease; preoperative mini-mental state examination (MMSE) scores was lower than 17 for illiterate, 20 for individuals with 1–6 years of education, 24 for individuals with seven or more years of education; nerve block contraindications (needle insertion site infection, local anesthetic allergy, coagulation dysfunction, international normalized ratio > 1.4, platelet count $< 80 \times 10^9$ μl); pathological fracture; metabolic bone disease; old fracture dementia; a stroke within 6 months; transferred to the intensive care unit (ICU) after surgery; difficulty communicating; and/or drug or alcohol abuse.

Preoperative assessment

Baseline characteristics were collected 1 day before surgery, including patient demographic characteristics (e.g., sex, age, height, and weight), clinical characteristics (e.g., ASA grade, patient's history of circulatory system, respiratory system, nervous system, and endocrine system), cognitive function status measured using the MMSE (19), and sleep quality measured using the Pittsburgh Sleep Quality Index (20). The age-adjusted Charlson comorbidity index (ACCI) scores (21) were calculated.

Blood sample collection and biochemical analysis

We collected 2 ml of blood in a vacutainer (BD Biosciences, San Jose, CA, USA), which used EDTAK2 as an anticoagulant, after preoperative radial artery catheterization, and the blood sample was taken at 6:00 a.m. on the first day after surgery. The samples were centrifuged at 4,000 rpm/min for 10 min, and the supernatant was removed

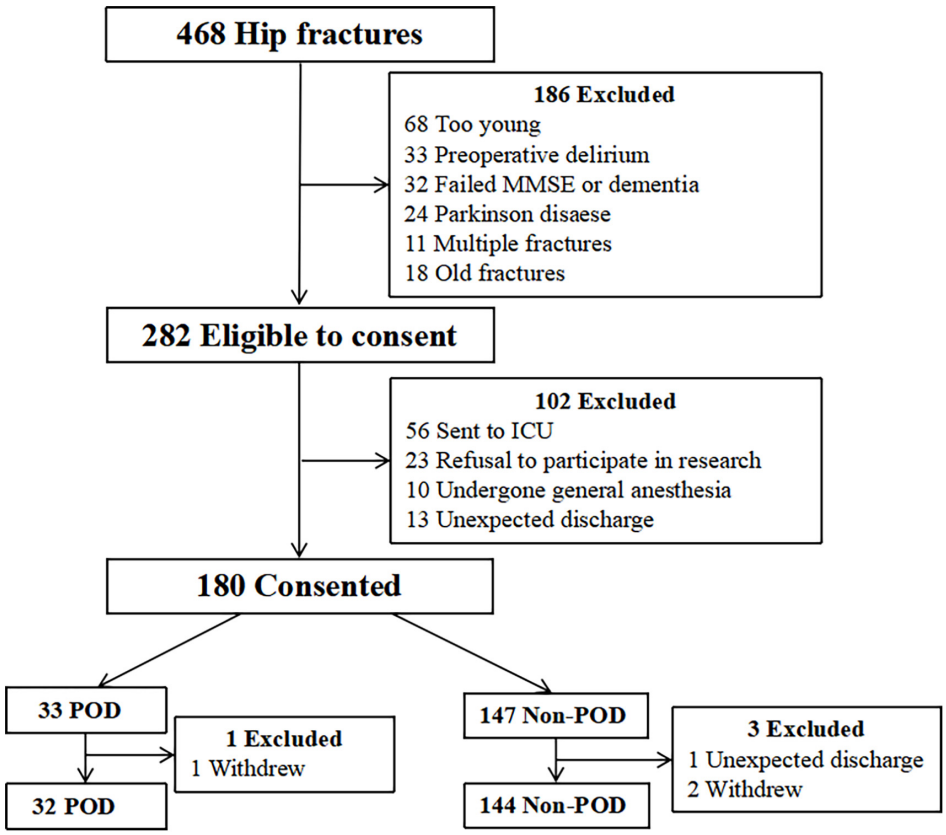

FIGURE 1
Study flow chart. Four hundred sixty-eight patients were initially screened for the study, and 176 patients were finally included in the data analysis. MMSE, mini-mental state examination; ICU, intensive care unit; POD, postoperative delirium.

and used for detection or it was aliquoted and frozen −80°C until analysis.

The visfatin plasma concentration was measured using the enzyme immunoassay method (RayBiotech, Norcross, GA, USA) that had a lower limit of detection of 0.778 ng/ml. Albumin, creatinine, thyroid stimulating hormone (TSH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) levels were tested using a blood biochemical analyzer (HITACHI, Tokyo, Japan); white blood cells (WBCs), red blood cells (RBCs), platelets, and hemoglobin levels were tested

TABLE 1 Associations between perioperative variables and postoperative delirium.

	Non-POD group (n = 144)	POD group (n = 32)	Statistical test (t /χ^2/z)	P-value
Preoperative data				
Age (years)	76.8 ± 7.9	82.5 ± 7.4	−3.7	<0.001**
Sex (female)	110 (76.4%)	22 (68.8%)	0.8	0.367
BMI (kg/m^2)	23.4 ± 3.8	23.2 ± 3.0	0.4	0.705
ASA physical status class			0.1	0.796
II	91 (63.2%)	21 (65.6%)		
III	53 (36.8%)	11 (34.4%)		
Education (years)	9.4 ± 4.1	9.3 ± 4.4	0.1	0.889
MMSE score (points)	25.5 ± 1.3	24.5 ± 1.0	4.9	<0.001**
ADL score (points)	92.9 ± 13.5	92.0 ± 10.5	0.4	0.718
PSQI score (points)	13.2 ± 5.7	15.2 ± 5.2	−1.8	0.077
ACCI score (points)	4.3 ± 1.4	4.9 ± 1.4	−2.1	0.040*
Admission–Operation time(hours)	32.5 (27.0, 45.0)	35.0 (27.0, 45.0)	−0.1	0.946
Ischemic heart disease	35 (24.3%)	8 (25.0%)	< 0.1	0.934
Chronic obstructive pulmonary disease	8 (5.6%)	1 (3.1%)	0.3	0.572
Hypertension	68 (47.2%)	21 (65.6%)	3.5	0.060
Diabetes	44 (30.6%)	8 (25.0%)	0.4	0.533
Stroke	29 (20.1%)	3 (9.4%)	2.0	0.153
Blood glucose (mmol/L)	8.6 ± 3.0	8.3 ± 2.7	0.7	0.504
Glycated hemoglobin (%)	6.5 ± 1.7	6.3 ± 1.2	0.4	0.670
Albumin (g/L)	40.4 ± 5.1	40.6 ± 3.3	−0.3	0.795
Creatinine (mmol/L)	68.0 ± 34.7	70.5 ± 28.5	−0.4	0.713
TSH (mIU/L)	2.8 ± 6.4	4.7 ± 16.1	−0.6	0.538
AST (IU/L)	22.9 ± 9.7	24.2 ± 9.3	−0.7	0.505
ALT (IU/L)	18.5 ± 8.6	21.6 ± 13.4	−1.2	0.230
WBC (×10^9 /L)	10.2 ± 3.2	11.1 ± 2.6	−1.6	0.111
RBC (×1012/L)	4.1 ± 0.6	4.1 ± 0.6	0.3	0.781
Platelet (×10^9 /L)	198.4 ± 53.5	202.8 ± 56.6	−0.4	0.685
Hemoglobin (g/L)	126.2 ± 16.7	125.1 ± 18.6	0.3	0.759
Visfatin (ng/ml)	43.2 (30.5, 70.7)	44.4 (20.5, 112.6)	−0.2	0.848
Preoperative plasma IL-1β (pg/ml)	26.5 (9.4, 59.1)	24.1 (1.8, 44.6)	−0.9	0.375
Preoperative plasma IL-6 (pg/ml)	9.5 (0.5, 22.7)	20.2 (0.1, 40.8)	−1.2	0.215
Intraoperative data				
Duration of surgery (min)	62.6 ± 26.4	55.2 ± 16.3	1.5	0.139
Duration of anesthesia (min)	88.0 ± 28.4	79.2 ± 17.7	1.7	0.100
Blood loss (ml)	200.0 (100.0, 300.0)	200.0 (100.0, 300.0)	−1.2	0.242
Postoperative items				
Postoperative serum IL-1β (pg/ml)	18.3 (1.4, 40.5)	13.6 (0.5, 30.7)	−1.0	0.315
Postoperative serum IL-6 (pg/ml)	101.5 (41.6, 186.3)	167.5 (121.1, 262.7)	−3.1	0.002
Hospitalization days	3.0 (3.0, 4.0)	3.0 (3.0, 4.0)	−0.7	0.480

Categorical variables are expressed as the n (%). Normally distributed data are presented as the mean ± SD, whereas, non-normally distributed data are expressed as the median (25th percentile, 75th percentile). BMI, body mass index; ASA, American Society of Anesthesiologists; MMSE, mini-mental state examination; ADL, activities of daily living; PSQI, Pittsburgh sleep quality index; ACCI, age-adjusted Charlson comorbidity index; TSH, thyroid stimulating hormone; AST, aspartate aminotransferase; ALT, alanine aminotransferase; WBC, white blood cell; RBC, red blood cell; IL-1β, interleukin-1β; IL-6, interleukin-6; SD, standard deviation. *$p < 0.05$, **$p < 0.01$.

using a blood analyzer (SYSMEX, Kobe, Japan). IL-1β and IL-6 levels were also tested using an immunosorbent assay (Boster, Wuhan, China).

Anesthesia and analgesia

After admission, the geriatric doctor evaluated the pain of the patients before surgery. If the Numerical Rating Scale (NRS) score was greater than three, the patient would be given administrative drug Tylenine (containing oxycodone hydrochloride 5 mg and acetaminophen 325 mg) or Dolantin 50 mg according to their physical conditions.

Fascia iliaca block and subarachnoid spinal anesthesia was used. After entering the surgical theater, echocardiogram monitoring, invasive blood pressure through radial artery catheterization, and pulse oximetry monitoring were performed. All patients received ultrasound-guided fascia iliaca block before surgery and were administered 30 ml of 0.4% ropivacaine. For spinal anesthesia, the L2–3 or L3–4 levels was selected to puncture, and 8–10 mg of 0.3% ropivacaine was used, and no epidural catheter was placed.

All patients were treated with patient-controlled intravenous analgesia after surgery. The drug regimen was as follows: sufentanil 0.1 μg/kg, flurbiprofen axetil 200 mg, tropisetron hydrochloride 10 mg and normal saline to a volume of 100 ml. When the postoperative NRS pain scores was greater than three points or the patient actively requested additional analgesia because they were experiencing pain, the rescue analgesic drug Tylenine or Dolantin 50 mg was administered (22).

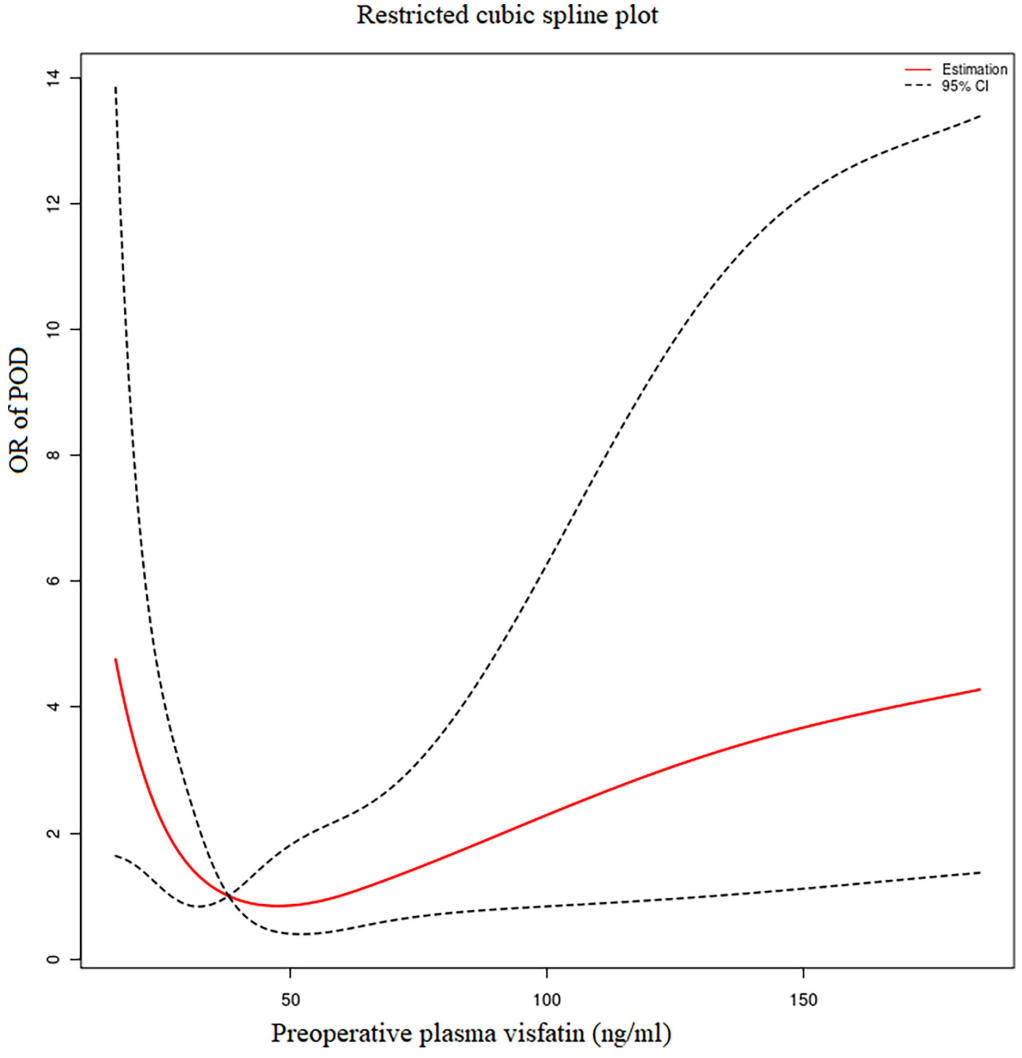

FIGURE 2
Restricted cubic spline analysis results. The relationship between the preoperative visfatin levels and OR of POD. OR, odd ratio; POD, postoperative delirium.

Delirium assessment

The 3-min diagnostic interview for Confusion Assessment Method (3D-CAM) is an efficient and reliable way to determine whether a patient has delirium. The 3D-CAM assessment can be completed in an average of 3 min, and it has excellent performance compared with other evaluation methods. Its sensitivity and specificity are about 84.6–87.2% and 96.7–97.4%, respectively (23). A geriatrician trained by a professional psychiatrist performed 3D-CAM assessments twice daily (morning and afternoon) on patients during the first two postoperative days (24).

Sample size

A piecewise regression model was used in the present study to examine the association between preoperative visfatin and POD. Five events per variable (EPV) is a widely used minimum criterion for sample size considerations in regression analysis. It was estimated that five variables could be included in the final model. For a given number of EPVs, 5 × EPV events are required in the analysis sample. For an EPV value of five, at least 25 events (development of POD) were required for the analysis. With an anticipated dropout rate of 10%, 28 POD patients were required. Additionally, a previous study showed that approximately 16% of patients who underwent hip replacement surgery developed POD, and thus, a minimum sample size of 176 was required for this study.

Statistical analysis

Analysis was performed using SPSS v.25.0 (IBM Corp., Armonk, NY, USA) and R statistical software (version 4.2.0, R Core Team, Vienna, Austria). The intergroup comparison for normally distributed measurement data was performed using an independent sample *t*-test, and the results are presented as the mean and standard deviation (SD). Measurement data with a skewed distribution was presented as the median (quartile), and the intergroup comparison was performed using the Mann–Whitney U-test. Categorical variables were described using the frequency (%), and the intergroup comparisons were described using Pearson chi-square or Fisher's exact probability test. Logistic regression was used for multivariate analysis. The correlation between visfatin and IL-6 is based on the Pearson or Spearman analysis.

Restricted cubic splines were used to analyze the association between preoperative plasma visfatin and the risk of POD. When there was evidence of non-linearity, a piecewise regression model was next fitted. The package segmented (version 1.4-1) was used to fit piecewise regression models, while adjusting for covariates. Mediation analysis was using mediation package (25).

Results

Patients characteristics

Among 176 patients who underwent hip fracture surgery, 18.2% (32 of 176) developed POD in our study population. The average age of patients in the POD group was 82.5 ± 7.4 years, which was significantly older than that of patients in the non-POD group (76.8 ± 7.9 years, $p < 0.01$). There were sixty-six (23.6%) and 10 (31.2%) men in the non-POD

TABLE 2 Pearson correlation analysis between visfatin and inflammation factors when visfatin concentrations was lower than 37.87 ng/ml.

		Preoperative plasma visfatin
Preoperative plasma IL-1β	Correlation coefficient	−0.10
	P-value	0.409
Preoperative plasma IL-6	Correlation coefficient	−0.10
	P-value	0.428
Postoperative plasma IL-1β	Correlation coefficient	−0.13
	P-value	0.323
Postoperative plasma IL-6	Correlation coefficient	0.03
	P-value	0.833

IL-1, interleukin-1; IL-6, interleukin-6.

TABLE 3 Pearson correlation analysis between visfatin and inflammation factors when visfatin concentrations was above 37.87 ng/ml.

		Preoperative plasma visfatin
Preoperative plasma IL-1β	Correlation coefficient	−0.12
	P-value	0.220
Preoperative plasma IL-6	Correlation coefficient	0.07
	P-value	0.470
Postoperative plasma IL-1β	Correlation coefficient	−0.12
	P-value	0.231
Postoperative plasma IL-6	Correlation coefficient	0.68**
	P-value	<0.001

IL-1, interleukin-1; IL-6, interleukin-6. *$p < 0.05$, **$p < 0.01$.

and POD groups, respectively, which was not significantly different ($p > 0.05$). Demographics such as gender, BMI, ASA, ADL, and education, did not show a group difference ($p > 0.05$). However, preoperative MMSE scores for patients in the POD group were significantly lower than those in the non-POD group ($p < 0.01$). Additionally, ACCI scores ($p = 0.04$) and postoperative plasma IL-6 levels ($p = 0.002$) were significantly higher in the POD group compared with that in the non-POD group. Other biochemical tests such as preoperative plasma glucose, creatinine, TSH, AST, ALT, WBC, RBC, and postoperative IL-1β levels showed no differences ($p > 0.05$). Additionally, preoperative plasma visfatin levels showed no difference between the two groups (Table 1).

Univariate logistic analysis showed that four factors, including age, preoperative MMSE scores, ACCI, and postoperative plasma IL-6, were statistically associated with POD in our research. Further multivariable analysis showed that three factors including age, low preoperative MMSE scores, and low postoperative plasma IL-6 levels were independent risk factors in POD among older hip fracture patients (Supplementary Table 1).

Among 32 POD patients, one patient had POD on the second day after operation (3.1%), and the other 31 patients had POD on the first day after operation (96.8%).

Correlation between preoperative plasma visfatin and postoperative delirium

Using R 4.2.0 software, we found the preoperative plasma visfatin concentrations had a non-linear relationship with the risk of POD, with an inflection point between 30 and 50 ng/ml (Figure 2). When the preoperative visfatin level was lower than that of the inflection point, the risk of POD decreases as the preoperative visfatin level increases. Above this inflection point, the risk of POD increases with increasing preoperative visfatin levels.

Break-point value by segmented regression

Segmented regression performed using R 4.2.0 software showed that the break-point value was 37.87 ng/ml. A decrease in the risk of POD was observed within the lower range until 37.87 ng/ml, with a hazard ratio of 0.59 per 5 ng/ml (OR = 0.59, 95% CI = 0.37–0.95), which increased thereafter (P for non-linearity < 0.001), with a hazard ratio of 1.116 per 10 ng/ml (OR = 1.10, 95% CI = 1.02–1.23).

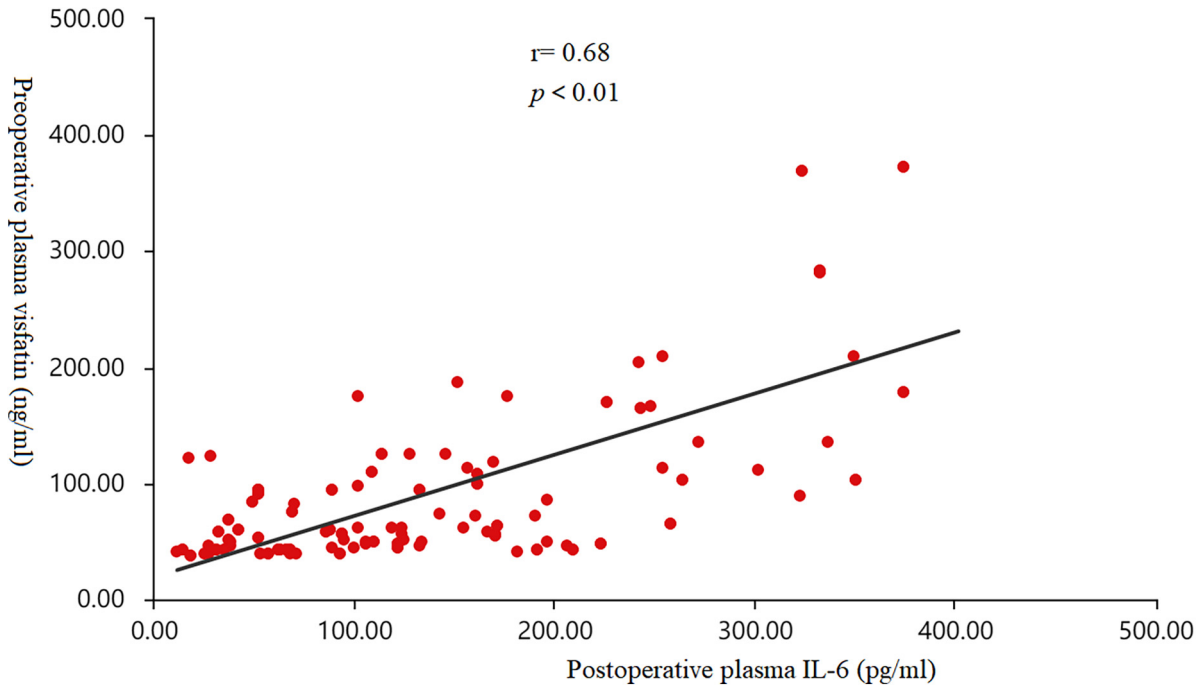

FIGURE 3
Scatter diagram. The correlation between the concentrations of preoperative plasma visfatin and postoperative plasma interleukin (IL-6) levels in patients with a plasma visfatin level of more than 37.87 ng/ml (r = 0.68, $p < 0.01$). IL-6, interleukin-6.

Pearson correlation analysis of the relationship between visfatin and inflammatory factors

Pearson correlation analysis were used to analyze the correlation between visfatin and inflammatory factors. When the concentrations of preoperative plasma visfatin was lower than 37.87 ng/ml, there was no correlation between visfatin and IL-6 or IL-1 (Table 2), but when the preoperative plasma visfatin level was higher than 37.87 ng/ml, there was a positive correlation between concentrations of preoperative plasma visfatin and concentrations of postoperative plasma IL-6 (Table 3). Their relationship showed in a scatter plot (Figure 3).

Mediation analysis of the relationship between visfatin, interleukin-6, and postoperative delirium

We further analyzed whether preoperative plasma visfatin can affect the occurrence of POD by regulating inflammatory using mediation analysis. When the concentration of visfatin was higher than 37.87 ng/ml, the total effect of preoperative plasma visfatin on POD (c) could be divided into direct effect (c') and indirect effect (a and b), the indirect effect was exerted by affecting postoperative plasma IL-6. Here, we use an easy model to show the relationship between them (Figure 4). The coefficients of total effect, direct effect and indirect effect were showed in Table 4.

Discussion

The results of our study show that visfatin has a dual effect on POD, when the concentration of preoperative visfatin is higher than 37.87 ng/ml, it may play a role by regulating the release of IL-6.

This study showed that increasing age, a low MMSE score, a high ACCI score, and high postoperative plasma IL-6 levels were independent risk factors for PODs. When the concentration of preoperative plasma visfatin was lower than 37.87 ng/ml, it was a negatively correlated with the risk of POD; when concentration was exceeded, it was positively correlated with the risk of POD, which was associated with postoperative plasma IL-6 levels.

Postoperative delirium is a serious complication, which can potentially lead to longer hospital stays and even permanent disabilities. Additionally, POD may increase the risk of delirium-related dementia. Many scholars have conducted researches to prevent and reduce the probability of POD occurrence. Some of our results are consistent with those of previous studies. Some studies showed that advanced age and multiple comorbidities are risk factors for POD (3, 26).

For the relationship between IL-6 and POD, many studies suggested that preoperative higher preoperative IL-6 blood levels were associated with POD occurrence (7, 27–29). However, our study did not show a difference in the preoperative plasma IL-6 concentration between the two groups, but the plasma IL-6 concentration on day one after surgery in the POD group was significantly higher than that in the non-POD group. This result may have occurred because we took

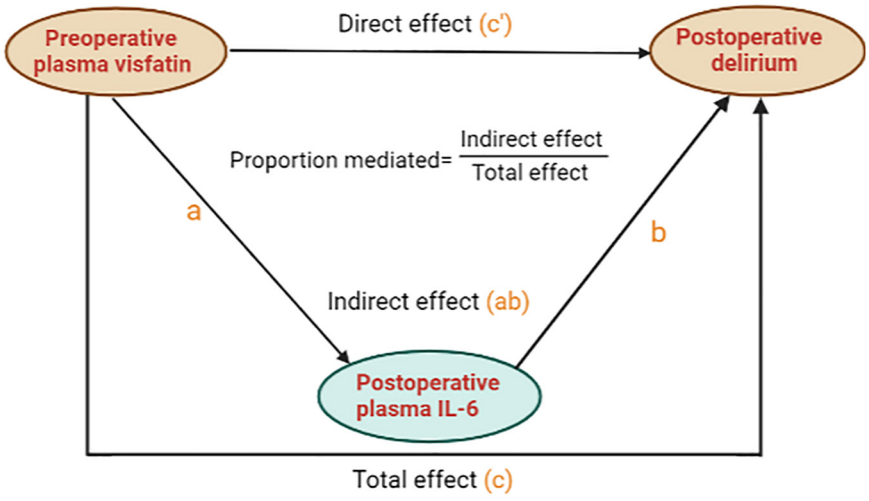

FIGURE 4
A mediation analysis model diagram. For brevity and clarity, a simplified version of the calculated model is presented. "c" means the total effect of preoperative plasma visfatin on postoperative delirium (POD) is represented by "c", whereas, "c"' means the direct effect of preoperative plasma visfatin on POD after controlling for the level of postoperative plasma interleukin (IL-6); "a" means the effect of preoperative plasma visfatin on the level of postoperative plasma IL-6; "b" means the effect of postoperative plasma IL-6 on POD, after controlling for preoperative plasma visfatin, the indirect effect of preoperative plasma visfatin on POD through postoperative plasma IL-6 can then be quantified as the product of "a" and "b". IL-6, interleukin-6; POD, postoperative delirium.

TABLE 4 Coefficients of mediation analysis.

Variables	POD					Postoperative serum IL-6					POD				
	B	Standard error	*t*	*β*	*p*	*B*	Standard error	*t*	*β*	*p*	*B*	Standard error	*t*	*β*	*p*
Constant	1.204	1.064	1.131	–	**0.261**	363.744	221.126	1.645	–	**0.104**	0.757	1.05	0.721	–	**0.473**
Age	0.011*	0.005	2.106	0.245	**0.038**	0.388	1.084	0.358	0.034	**0.721**	0.011*	0.005	2.07	0.235	**0.041**
MMSE	−0.074*	0.033	−2.244	−0.243	**0.027**	−11.74	6.875	−1.708	−0.152	**0.091**	−0.06	0.033	-83	−0.196	**0.071**
PSQI	−0.002	0.006	−0.32	−0.03	**0.75**	−0.437	1.296	−0.337	−0.026	**0.737**	−0.001	0.006	-0.24	−0.022	**0.811**
ACCI	−0.041	0.029	−1.404	−0.164	**0.164**	−0.646	6.077	−0.106	−0.01	**0.916**	−0.04	0.028	−1.416	−0.161	**0.16**
Hypertension	0.05	0.076	0.656	0.066	**0.514**	−15.808	15.841	−0.998	−0.082	**0.321**	0.069	0.075	0.931	0.091	**0.354**
Preoperative plasma visfatin	0.001**	0	2.871	0.271	**0.005**	0.846**	0.1	8.439	0.654	**0.000**	0	0.001	0.55	0.068	**0.584**
Postoperative plasma IL-6											0.001*	0	2.476	0.31	**0.015**
R^2			0.222					0.475					0.273		
Adjust R^2			0.17					0.439					0.215		

The mediation analysis of the relationship between visfatin, postoperative plasma IL-6 and POD. *B*, non standardized regression coefficient; *β*, standardized regression coefficient; *t*, B/Standard error. POD, postoperative delirium; IL-6, interleukin-6.
*$p < 0.05$, **$p < 0.01$. Bold values represent the *p*-value.

blood samples from the patients on the morning of surgery instead of blood samples when the patients were just admitted to the hospital. After admission, the patients took non-steroidal anti-inflammatory drugs and painkillers, which reduced the inflammation, resulting in a decrease in the IL-6 level.

Visfatin is nicotinamide phosphoribosyltransferase (NAMPT), which includes extracellular NAMPT (eNAMPT) and intracellular NAMPT (iNAMPT). iNAMP is mainly involved in glucose metabolism, and eNAMPT regulates inflammatory factor expression (30). The relationship between the visfatin level in blood and cognitive function remains controversial. Some studies showed that elevated blood visfatin levels are associated with a cognitive decline (12, 14, 31). However, some studies indicated that loss of visfatin may harm neurons and impair cognitive function (18). To date, there have no relevant studies on POD, and our study is the first to explore the relationship between visfatin and POD.

In this study, we did not find a correlation between visfatin and IL-6 when the preoperative plasma visfatin concentration was less than 37.87 ng/ml. It is worth exploring the effect of visfatin on POD when below 37.87 ng/ml.

Visfatin plays a crucial role in glucose metabolism. Visfatin activates its target cells by binding to the insulin receptor (IR) and exerts multiple insulin-mimetic effects, including enhanced glucose uptake and increased triglyceride synthesis (10, 32–34). A secondary analysis indicated that type 2 diabetes was associated with POD occurrence (35). An observational study showed that the average blood glucose and blood glucose variability within 48 h of POD in patients after acute aortic separation are significantly higher than those of non-POD patients (36), which indicated that blood glucose fluctuations may cause cognitive dysfunction in older patients. A high basal blood glucose level may cause direct neuron damage, and compared with long-term blood sugar fluctuations, short-term (acute) blood glucose fluctuations may cause more damage to neurons and lead to cognitive dysfunction (37). We hypothesized that visfatin effects at lower levels may occur through regulation of glucose metabolism, thereby affecting POD occurrence. Unfortunately, in this study, we did not record patients' blood glucose level at multiple time points during the perioperative period. We will next study the relationship between visfatin and the fluctuation of blood glucose.

Our study showed that an elevated visfatin concentration in the blood above a certain level will promote IL-6 expression and increase the risk of POD occurrence. Visfatin has a pro-inflammatory effect. Numerous studies have shown that visfatin activates monocytes to produce pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) (38–40). However, in our study, we did not detect other inflammatory factors such as TNF-α or C-reactive protein in patients' blood samples, so it is not possible to determine whether visfatin affects POD occurrence

by regulating other inflammatory factors. We will detect them in our future studies.

The main advantages of this study are as follows: our study is the first to explore the relationship between visfatin and POD. Our study exhibits that novel inflammatory factors "visfatin" has a dual effection on the occurrence of POD, which provides ideas for follow-up research and may provide some guidance for POD prediction. Furthermore, our study shows when visfatin concentration was higher than 37.87 ng/ml, it may affect POD through the medication effect on postoperative plasma IL-6. We demonstrated that there is a correlational relationship between high pre-operative visfatin levels, elevated post-operative levels of IL-6 and POD.

The main limitations of this study are as follows: (1) This study is a single center study with a relatively small sample size. In future studies, we will conduct a multi-center study; (2) the numbers of kinds of inflammatory factors detected in this study was too limited so we cannot make it clear that whether visfatin affect POD through other inflammatory factors (3) this study did not detect the central visfatin, and this issue will be investigated in our follow-up studies. (4) The patients in this study were discharged on the third day after surgery or transferred to the rehabilitation department for further treatment, so this study only evaluated the complications of 2 days after surgery. The follow-up study will observe and follow up the long-term prognosis of patients.

Conclusion

In summary, our study showed that there is a non-linear relationship between preoperative plasma visfatin and POD. Preoperative plasma visfatin has a dual effect on POD. Visfatin is the protective factor against POD when its preoperative plasma concentration is below 37.87 ng/ml. However, when it exceeds 37.87 ng/ml, the visfatin concentration becomes a risk factor for POD, which is mediated by postoperative plasma of IL-6.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving human participants were reviewed and approved by Beijing Jishuitan Hospital Medical Science Research Ethics Committee (JLKS202103-35). The patients/participants provided their written informed consent to participate in this study.

Author contributions

NK, YY, NY, GW, and XG contributed to the study design. XG, YY, NY, and ZL obtained the funding. WZ, GW, and YY performed the anesthesia. NK and KZ collected the blood samples, contributed to the data collection, and responsible for data statistics. JH, YL, LC, and YL are laboratory technicians. YH, YS, and NK verified the underlying data. NK and YY drafted the manuscript. XG, KZ, YY, and NY reviewed the manuscript. All authors read and approved the final version of the manuscript.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.1024942/full#supplementary-material

References

1. Chen FP, Shyu YC, Fu TS, Sun CC, Chao AS, Tsai TL, et al. Secular trends in incidence and recurrence rates of hip fracture: A nationwide population-based study. *Osteoporos Int.* (2017) 28:811–8. doi: 10.1007/s00198-016-3820-3

2. Gullberg B, Johnell O, Kanis JA. World-wide projections for hip fracture. *Osteoporos Int.* (1997) 7:407–13.

3. Wu J, Yin Y, Jin M, Li B. The risk factors for postoperative delirium in adult patients after hip fracture surgery: A systematic review and meta-analysis. *Int J Geriatr Psychiatry.* (2021) 36:3–14.

4. Austin CA, O'Gorman T, Stern E, Emmett D, Sturmer T, Carson S, et al. Association between postoperative delirium and long-term cognitive function after major nonemergent surgery. *JAMA Surg.* (2019) 154:328–34. doi: 10.1001/jamasurg.2018.5093

5. Maldonado JR. Delirium pathophysiology: An updated hypothesis of the etiology of acute brain failure. *Int J Geriatr Psychiatry.* (2018) 33:1428–57.

6. Needham MJ, Webb CE, Bryden DC. Postoperative cognitive dysfunction and dementia: What we need to know and do. *Br J Anaesth.* (2017) 119:i115–25.

7. Liu X, Yu Y, Zhu S. Inflammatory markers in postoperative delirium (POD) and cognitive dysfunction (POCD): A meta-analysis of observational studies. *PLoS One.* (2018) 13:e0195659. doi: 10.1371/journal.pone.0195659

8. Chen Y, Lu S, Wu Y, Shen Y, Zhao H, Ding S, et al. Change in serum level of interleukin 6 and delirium after coronary artery bypass graft. *Am J Crit Care.* (2019) 28:462–70.

9. Sonoli SS, Shivprasad S, Prasad CV, Patil AB, Desai PB, Somannavar MS. Visfatin–a review. *Eur Rev Med Pharmacol Sci.* (2011) 15:9–14.

10. Taskesen D, Kirel B, Us T. Serum visfatin levels, adiposity and glucose metabolism in obese adolescents. *J Clin Res Pediatr Endocrinol.* (2012) 4:76–81.

11. Heo YJ, Choi SE, Lee N, Jeon JY, Han SJ, Kim DJ, et al. Visfatin exacerbates hepatic inflammation and fibrosis in a methionine-choline-deficient diet mouse model. *J Gastroenterol Hepatol.* (2021) 36:2592–600. doi: 10.1111/jgh.15465

12. Huang HH, Chang JC, Liu HC, Yang ZY, Yang YJ, Chen LK, et al. Handgrip strength, tumor necrosis factor-alpha, interlukin-6, and visfatin levels in oldest elderly patients with cognitive impairment. *Exp Gerontol.* (2020) 142:111138. doi: 10.1016/j.exger.2020.111138

13. Kazem YM, Shebini SM, Moaty MI, Fouad S, Tapozada ST. Sleep deficiency is a modifiable risk factor for obesity and cognitive impairment and associated with elevated visfatin. *Open Access Maced J Med Sci.* (2015) 3:315–21. doi: 10.3889/oamjms.2015.063

14. Huang X, Wang C, Tian S, Huang R, Guo D, Zhang H, et al. Higher plasma level of nampt presaging memory dysfunction in chinese type 2 diabetes patients with mild cognitive impairment. *J Alzheimers Dis.* (2019) 70:303–14. doi: 10.3233/JAD-190269

15. Xing S, Hu Y, Huang X, Shen D, Chen C. Nicotinamide phosphoribosyltransferaserelated signaling pathway in early Alzheimer's disease mouse models. *Mol Med Rep.* (2019) 20:5163–71. doi: 10.3892/mmr.2019.10782

16. Sharifipour E, Sharifimoghadam S, Hassanzadeh N, Ghasemian Mojarad N, Ghoreishi A, Hejazi SA, et al. Altered plasma visfatin levels and insulin resistance in patients with Alzheimer's disease. *Acta Neurol Belg.* (2020) 120:901–6. doi: 10.1007/s13760-019-01084-9

17. Erfani S, Khaksari M, Oryan S, Shamsaei N, Aboutaleb N, Nikbakht F, et al. Visfatin reduces hippocampal CA1 cells death and improves learning and memory deficits after transient global ischemia/reperfusion. *Neuropeptides.* (2015) 49:63–8. doi: 10.1016/j.npep.2014.12.004

18. Stein LR, Wozniak DF, Dearborn JT, Kubota S, Apte RS, Izumi Y, et al. Expression of Nampt in hippocampal and cortical excitatory neurons is critical for cognitive function. *J Neurosci.* (2014) 34:5800–15. doi: 10.1523/JNEUROSCI.4730-13.2014

19. Girard TD, Thompson JL, Pandharipande PP, Brummel NE, Jackson JC, Patel MB, et al. Clinical phenotypes of delirium during critical illness and severity of subsequent long-term cognitive impairment: A prospective cohort study. *Lancet Respir Med.* (2018) 6:213–22. doi: 10.1016/S2213-2600(18)30062-6

20. Buysse DJ, Reynolds CF III, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: A new instrument for psychiatric practice and research. *Psychiatry Res.* (1989) 28:193–213. doi: 10.1016/0165-1781(89)90047-4

21. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol.* (1994) 47:1245–51.

22. Yuan Y, Li Z, Yang N, Han Y, Ji X, Han D, et al. Exosome alpha-Synuclein release in plasma may be associated with postoperative delirium in hip fracture patients. *Front Aging Neurosci.* (2020) 12:67. doi: 10.3389/fnagi.2020.00067

23. Marcantonio ER, Ngo LH, O'Connor M, Jones RN, Crane PK, Metzger ED, et al. 3D-CAM: Derivation and validation of a 3-minute diagnostic interview for CAM-defined delirium: A cross-sectional diagnostic test study. *Ann Intern Med.* (2014) 161:554–61. doi: 10.7326/M14-0865

24. Prins TW, Scholtens IM, Bak AW, van Dijk JP, Voorhuijzen MM, Laurensse EJ, et al. Data on screening and identification of genetically modified papaya in food supplements. *Data Brief.* (2016) 9:43–6.

25. Fisher P, Cao W, Yu Q. Using SAS macros for multiple mediation analysis in R. *J Open Res Softw.* (2020) 8:22. doi: 10.5334/jors.277

26. Yang Y, Zhao X, Dong T, Yang Z, Zhang Q, Zhang Y. Risk factors for postoperative delirium following hip fracture repair in elderly patients: A systematic review and meta-analysis. *Aging Clin Exp Res.* (2017) 29:115–26. doi: 10.1007/s40520-016-0541-6

27. Noah AM, Almghairbi D, Evley R, Moppett IK. Preoperative inflammatory mediators and postoperative delirium: Systematic review and meta-analysis. *Br J Anaesth.* (2021) 127:424–34.

28. Capri M, Yani SL, Chattat R, Fortuna D, Bucci L, Lanzarini C, et al. Pre-Operative, high-IL-6 blood level is a risk factor of post-operative delirium onset in old patients. *Front Endocrinol.* (2014) 5:173. doi: 10.3389/fendo.2014.00173

29. Neerland BE, Hall RJ, Seljeflot I, Frihagen F, MacLullich AM, Raeder J, et al. Associations between delirium and preoperative cerebrospinal fluid C-reactive protein, interleukin-6, and interleukin-6 receptor in individuals with acute hip fracture. *J Am Geriatr Soc.* (2016) 64:1456–63. doi: 10.1111/jgs.14238

30. Carbone F, Liberale L, Bonaventura A, Vecchie A, Casula M, Cea M, et al. Regulation and function of extracellular nicotinamide phosphoribosyltransferase/visfatin. *Compr Physiol.* (2017) 7: 603–21.

31. Zeng M, Wei TF, Chen C, Shen C, Gao TY, Xie X, et al. Nicotinamide phosphoribosyltransferase inhibitor ameliorates mouse aging-induced cognitive impairment. *J Cereb Blood Flow Metab.* (2021) 41:2510–23. doi: 10.1177/0271678X211006291

32. Liang Z, Wu Y, Xu J, Fang Q, Chen D. Correlations of serum visfatin and metabolisms of glucose and lipid in women with gestational diabetes mellitus. *J Diabetes Investig.* (2016) 7:247–52.

33. Jian WX, Luo TH, Gu YY, Zhang HL, Zheng S, Dai M, et al. The visfatin gene is associated with glucose and lipid metabolism in a Chinese population. *Diabet Med.* (2006) 23:967–73. doi: 10.1111/j.1464-5491.2006.01909.x

34. Lee JO, Kim N, Lee HJ, Lee YW, Kim JK, Kim HI, et al. Visfatin, a novel adipokine, stimulates glucose uptake through the Ca2 +-dependent AMPK-p38 MAPK pathway in C2C12 skeletal muscle cells. *J Mol Endocrinol.* (2015) 54:251–62. doi: 10.1530/JME-14-0274

35. Liu K, Song Y, Yuan Y, Li Z, Wang X, Zhang W, et al. Type 2 diabetes mellitus with tight glucose control and poor pre-injury stair climbing capacity may predict postoperative delirium: A secondary analysis. *Brain Sci.* (2022) 12:951. doi: 10.3390/brainsci12070951

36. Yuan SJ, Shen J. Increased preoperative glucose variability is associated with adverse perioperative outcomes following orthopedic surgery in patients with type 2 diabetes mellitus. *Curr Med Sci.* (2020) 40:523–9. doi: 10.1007/s11596-020-2209-x

37. Lin YJ, Lin LY, Peng YC, Zhang HR, Chen LW, Huang XZ, et al. Association between glucose variability and postoperative delirium in acute aortic dissection patients: An observational study. *J Cardiothorac Surg.* (2021) 16:82. doi: 10.1186/s13019-021-01456-4

38. Liu SW, Qiao SB, Yuan JS, Liu DQ. Visfatin stimulates production of monocyte chemotactic protein-1 and interleukin-6 in human vein umbilical endothelial cells. *Horm Metab Res.* (2009) 41:281–6.

39. Gong YY, Peng HY. Correlation analysis of epicardial adipose tissue thickness, C-reactive protein, interleukin-6, visfatin, juxtaposed with another zinc finger protein 1, and type 2 diabetic macroangiopathy. *Lipids Health Dis.* (2021) 20:25. doi: 10.1186/s12944-021-01451-7

40. Liu SW, Qiao SB, Liu DQ. [Visfatin promotes production of monocyte chemotactic protein-1 and interleukin-6 in human endothelial cells via insulin receptor]. Zhonghua Yi Xue Za Zhi. (2009) 89: 2843–6.

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Intraoperative electroencephalogram patterns as predictors of postoperative delirium in older patients: a systematic review and meta-analysis

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Background: Postoperative delirium (POD) significantly affects patient outcomes after surgery, leading to increased morbidity, extended hospital stays, and potential long-term cognitive decline. This study assessed the predictive value of intraoperative electroencephalography (EEG) patterns for POD in adults.

Methods: This systematic review and meta-analysis followed the PRISMA and Cochrane Handbook guidelines. A thorough literature search was conducted using PubMed, Medline, and CENTRAL databases focusing on intraoperative native EEG signal analysis in adult patients. The primary outcome was the relationship between the burst suppression EEG pattern and POD development.

Results: From the initial 435 articles identified, 19 studies with a total of 7,229 patients were included in the systematic review, with 10 included in the meta-analysis (3,705 patients). In patients exhibiting burst suppression, the POD incidence was 22.1% vs. 13.4% in those without this EEG pattern (p=0.015). Furthermore, an extended burst suppression duration associated with a higher likelihood of POD occurrence ($p = 0.016$). Interestingly, the burst suppression ratio showed no significant association with POD.

Conclusions: This study revealed a 41% increase in the relative risk of developing POD in cases where a burst suppression pattern was present. These results underscore the clinical relevance of intraoperative EEG monitoring in predicting POD in older patients, suggesting its potential role in preventive strategies.

Systematic Review Registration: This study was registered on International Platform for Registered Protocols for Systematic Reviews and Meta-Analyses: INPLASY202420001, https://doi.org/10.37766/inplasy2024.2.0001.

KEYWORDS

postoperative delirium, intraoperative EEG, burst suppression, systematic review, meta-analysis, surgery, anesthesia

1 Introduction

Postoperative delirium (POD) emerges as a multifaceted organic cerebral syndrome, presenting itself as a neuropsychiatric complication following surgical procedures (World Health Organisation, 1994). Marked by abrupt shifts in attention, cognition, and consciousness, POD poses a considerable challenge in perioperative care (O'Regan et al., 2013; Berikashvili et al., 2023). Its implications include heightened patient morbidity, prolonged hospitalization, and an elevated susceptibility to long-term cognitive decline, especially in older patients (Yan et al., 2023).

Given the organic underpinnings of postoperative delirium, monitoring brain activity through electroencephalography (EEG) during surgery emerges as a valuable approach for predicting this complication (Sun et al., 2020). Consequently, recent European guidelines on postoperative delirium management advocate for intraoperative monitoring of anesthesia depth and EEG patterns, specifically the burst suppression pattern, despite the limited quality of evidence supporting this recommendation (Aldecoa et al., 2023).

While a recent meta-analysis suggests that anesthesia guided by bispectral index (BIS) has not significantly reduced the incidence of postoperative delirium (Chew et al., 2022), it is crucial to recognize that excessively deep anesthesia remains a critical risk factor for its development (Evered et al., 2021). The pathological processes induced by overly deep anesthesia, contributing to the clinical manifestation of postoperative delirium, could potentially be discerned through the identification of EEG burst suppression patterns. Moreover, various other EEG signal characteristics may serve as potential predictors of postoperative delirium (Baron Shahaf et al., 2023; Khalifa et al., 2023; Kinoshita et al., 2023). Further research and exploration of EEG monitoring techniques hold promise in refining our understanding and prediction of postoperative delirium in clinical practice.

This systematic review and meta-analysis aim to assess the predictive value of intraoperative EEG for postoperative delirium in adults.

2 Materials and methods

This study was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Liberati et al., 2009) and Cochrane Handbook guidelines (Higgins et al., 2019). The meta-analysis protocol was registered with the International Platform for Registered Protocols for Systematic Reviews and Meta-Analyses (INPLASY) under registration number INPLASY202420001, https://doi.org/10.37766/inplasy2024.2.0001. The completed PRISMA checklist is presented in Supplementary Table S1.

2.1 Search strategy

A comprehensive systematic search was conducted to identify relevant studies published between January 1, 2003, and October 23, 2023. This search encompassed databases such as PubMed, Medline, and the Cochrane Central Register of Controlled Trials (CENTRAL) and was performed by three independent researchers. Additionally, the authors employed forward and backward snowballing methods [Litmaps service (Literature Map Software for Lit Reviews and Research and Litmaps, 2024)]. We did not restrict the search by language. The detailed search strategy and queries are available in Supplementary Appendix A.

2.2 Eligibility criteria and study selection

After the automatic exclusion of duplicate records, three researchers independently screened the remaining studies for eligibility based on their titles and abstracts utilizing the PICOS criteria (detailed in Supplementary Appendix B). We focused on prospective and retrospective observational studies that explored predictors of POD using intraoperative native EEG signal analysis in adult patients. The final inclusion in this study was determined after a thorough full-text article analysis. Studies were excluded if they met one of the following criteria: (1) were review articles, case reports or letters to the editors; (2) followed EEG-guided anesthesia; (3) reported no outcome data; (4) utilized non-intraoperative EEG; or (5) evaluated the BIS.

Any disagreements were resolved by consultation with the involvement of the supervisor until a consensus was reached.

2.3 Outcome measures and data extraction

For this review, a dedicated data collection form was developed. This form was utilized independently by three authors to independently assess the full manuscripts and supplemental or additional files of all included studies and extract the data. The following data were extracted: study design, sample size, first author, publication year, journal name, POD assessment method, study setting, participant age and sex, American Society of Anesthesiologists (ASA) score, type of anesthesia used, duration of surgery and anesthesia, length of intensive care unit (ICU) and hospital stay, intraoperative EEG timing, and the types and characteristics of EEG patterns in both the POD and non-POD groups. After independent data extraction, the researchers consulted with each other to identify disagreements and reach consensus through discussion.

In instances where the data were presented solely in graphical format, numerical values were extracted using the WebPlotDigitizer tool (Rohatgi, 2010). For studies presenting continuous data in non-standard formats (e.g., median, interquartile range, or 95% confidence intervals), we employed established methods to calculate the mean ± standard deviation (SD). These methods included the statistical techniques proposed by Wan et al. (2014) and Luo et al. (2018), as well as the Cochrane Handbook recommendations 6.5.2.2 and 6.5.2.5 (Higgins and Green, 2011).

This meta-analysis specifically focused on the burst suppression pattern in EEG signals, examining its duration, ratio, and presence (incidence). In this meta-analysis, the BSR is defined as the time EEG shows BSP divided by the total EEG monitoring time. This

differs from the clinical BSR, typically a time-varying percentage of BSP over a short period. Our BSR calculation reflects the overall incidence of burst suppression during the entire EEG session, providing a distinct measure for our analysis.

2.4 Data analysis and synthesis

In this meta-analysis, STATA 17.0 (StataCorp LLC, Texas, US) was used for both calculations and visualizations. We assessed interstudy heterogeneity using the I-squared (I^2) statistic and the Cochrane Q test. Standardized mean differences (SMDs) with 95% confidence intervals (CIs) were calculated for quantitative data. In accordance with the Cochrane handbook guidelines, SMDs were categorized into effect sizes: small (<0.40), moderate (0.40 to 0.70), and large (>0.70) (Higgins and Green, 2011). For categorical outcomes, logarithmic odds ratios (log ORs) and 95% CIs were determined.

A fixed-effects inverse-variance model was applied in cases of low statistical heterogeneity ($I^2 < 60\%$ and $p > 0.05$), while a random-effects model [restricted maximum likelihood (REML)] was used for $I^2 \geq 60\%$ and/or $p < 0.05$. Statistical significance was set at $p < 0.05$.

The diagnostic accuracy of burst suppression presence was evaluated through pooled metrics, sensitivity, specificity, and positive and negative likelihood ratios, along with the summary receiver operating characteristic (SROC) area under the curve (AUC), employing the 'midas' module in STATA 17.0 (Dwamena, 2007). All the EEG patterns were categorized into six distinct groups based on the specific characteristics of the EEG signals being studied: (1) wave patterns (alpha, beta, delta, theta), (2) burst suppression pattern, and (3) unclassified patterns (Supplementary Table S6). We calculated a weighted average AUCs for the wave patterns.

2.5 Internal validity and risk of bias assessment

The internal validity and risk of bias were assessed by two independent reviewers using the "Tool to assess risk of bias in cohort studies" contributed by the CLARITY Group at McMaster University (CLARITY-group. Tool to Assess Risk of Bias in Case Control Studies Hamilton, 2023). An explanation of the risk of bias assessment is presented in Supplementary Table S2. The results were visualized using the "risk-of-bias visualization tool" (McGuinness and Higgins, 2021). Publication bias and small-study effects were assessed using Egger's test and funnel plot analysis.

The certainty of evidence was assessed with the GRADE systematic approach (Guyatt et al., 2008).

2.6 Sensitivity analysis

For sensitivity analysis and a more convenient way of comparing effect sizes, direct mean difference (MD), odds ratio (OR) and risk ratio (RR) values were additionally calculated and analyzed.

3 Results

3.1 Study characteristics

In the initial search, a total of 435 articles were identified. Following an abstract screening process, 51 articles were selected for full-text evaluation. After careful reading of the full-text articles, 32 studies were excluded (Supplementary Table S3). Ultimately, this systematic review included 19 studies published between 2015 and 2023 (Soehle et al., 2015; Fritz et al., 2016; Hesse et al., 2019; Momeni et al., 2019; Pedemonte et al., 2020; Jung et al., 2021; Koch et al., 2021, 2023; Lele et al., 2022; Li et al., 2022; Lutz et al., 2022; Röhr et al., 2022; Windmann et al., 2022; Baron Shahaf et al., 2023; Dragovic et al., 2023; Khalifa et al., 2023; Kinoshita et al., 2023; Reese et al., 2023; Ostertag et al., 2024). Additionally, 10 of these articles were included in the meta-analysis (Soehle et al., 2015; Hesse et al., 2019; Pedemonte et al., 2020; Jung et al., 2021; Koch et al., 2021, 2023; Lele et al., 2022; Lutz et al., 2022; Röhr et al., 2022; Ostertag et al., 2024). A flowchart illustrating the study selection process is presented in Figure 1.

In this systematic review, a total of 7,229 patients were analyzed, comprising 1,370 patients with POD (POD+) and 5,859 without (POD-). The data extracted from the included articles are detailed in Supplementary Tables S4–S6. The characteristics of the studies included in the meta-analysis are summarized in Table 1. In the meta-analysis of 3,705 patients, 18.8% (696) developed POD. The meta-analysis included five prospective observational studies, two *post-hoc* analyses of randomized trials, two retrospective observational studies, and one *post-hoc* analysis of a prospective observational trial. The mean age ranged from 59.8 to 72.9 years, and the proportion of patients with ASA III-V varied from 23.7% to 95.6% (Table 1).

3.2 Presence of burst suppression

According to a meta-analysis of five studies encompassing 1,182 patients and reporting the burst suppression episodes on EEG, the incidence was significantly higher in patients who experienced POD (22.1% vs. 13.4%) [OR = 1.68 (1.22; 2.32), $p = 0.015$; log OR = 0.52 (0.2; 0.84), $p = 0.002$; RR = 1.41 (1.1; 1.8), $p = 0.006$] (Figure 2, Table 2, Supplementary Figures S1-S3).

The area under the SROC curve for the presence of burst suppression was 0.620 (0.580; 0.660) (Figure 3), with a pooled sensitivity of 0.60 (0.34; 0.81) and a specificity of 0.59 (0.35; 0.79) (Supplementary Figure S4).

3.3 Duration of burst suppression

According to a pooled analysis of five studies reporting this outcome and involving 1,568 patients, patients who experienced POD had a significantly extended duration of burst suppression on EEG [MD = 15.86 (3.02; 28.70) minutes, $p = 0.016$; SMD = 0.36 (0.23; 0.49), $p < 0.001$] (Table 2, Supplementary Figures S5, S6).

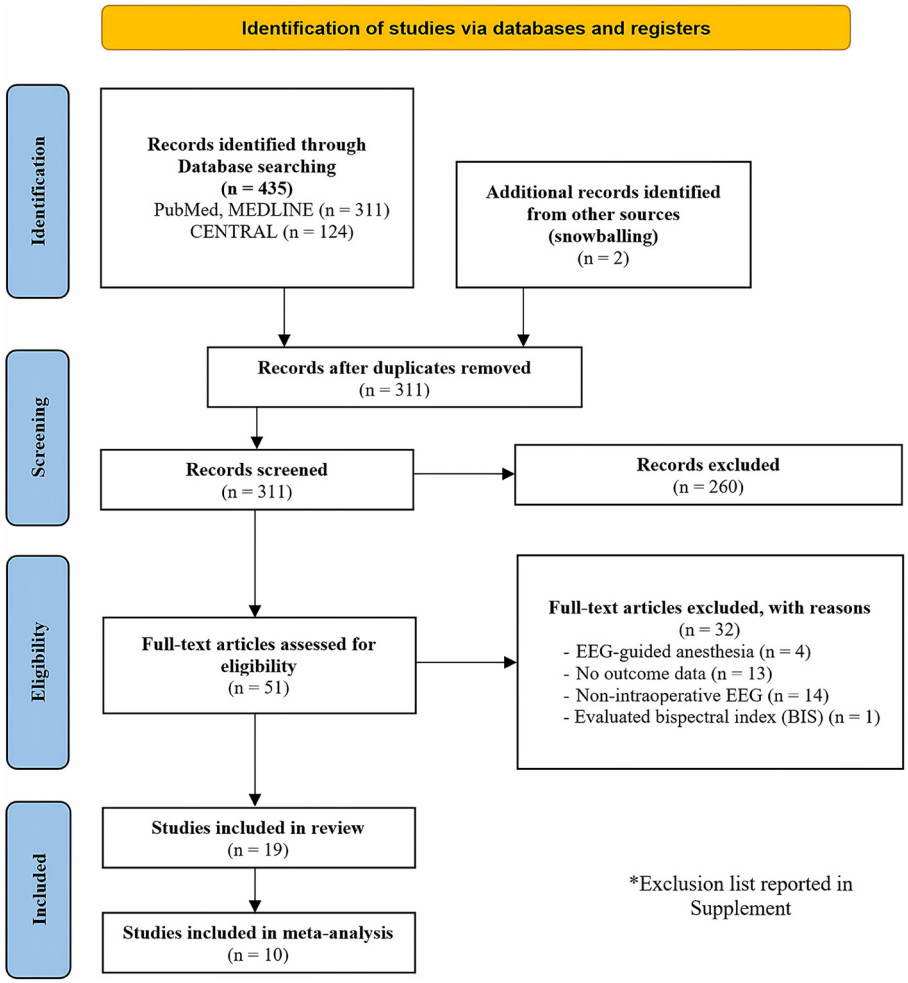

FIGURE 1
PRISMA flow diagram for study selection.

3.4 Burst suppression ratio

In a pooled analysis of two studies involving 2,125 patients and reporting the burst suppression ratio on EEG, we found no significant relationship with POD [MD = 0.007 (−0.004; 0.018), p = 0.217; SMD = 0.07 (−0.04; 0.18), p = 0.215] (Table 2, Supplementary Figures S7, S8).

3.5 Weighted average AUC values

The weighted average AUC values for the alpha (0.676), beta (0.670), delta (0.660), and theta (0.685) wave patterns were determined from studies included in the systematic review (Supplementary Table S6).

3.6 Risk of bias and GRADE assessment

The overall risk of bias of the 10 enrolled studies was judged as 'low' in three studies and 'some concerns' in 7 studies (Supplementary Figure S9). The main sources of bias identified were the lack of matching for confounding variables and inconsistency in exposure assessment. Egger's test and funnel plot analysis did not reveal small-study effects for the majority of the study outcomes (Supplementary Figure S10). Publication bias was statistically significant for the presence of burst suppression (Table 2, Supplementary Figure S10). According to the GRADE approach, a moderate level of evidence supported the association between duration of burst suppression and POD, while evidence for the incidence of burst suppression was considered very low (Supplementary Table S7).

4 Discussion

4.1 Key findings

This is the first systematic review and meta-analysis to evaluate various aspects of burst suppression pattern of EEG signals as prognostic factors of postoperative delirium in older adults. The meta-analysis revealed that the duration of burst suppression is

TABLE 1 Characteristics and description of the 10 trials included in the meta-analysis.

Study	Design	Journal	Sample size (All)	POD+ (N)	POD− (N)	Sex, male %	Age, mean	ASA III-V, %	POD assessment method	EEG pattern
Lele et al. (2022)	ROS	J Neurosurg Anesthesiol	112	10	102	54.5	59.8	ND	CAM	PBS; DBS
Jung et al. (2021)	POS	Medicine (Baltimore)	80	13	67	59.0	66.3	45.0	3D-CAM	DBS
Pedemonte et al. (2020)	ROS	Anesthesiology	159	23	136	69.0	70.1	95.6	CAM	PBS
Ostertag et al. (2024)	POS p-h	Anesthesiology	169	32	137	75.1	61.7	23.7	CAM-ICU	PBS
Soehle et al. (2015)	POS	BMC Anesthesiol	81	26	55	70.4	72.9	ND	CAM-ICU	DBS
Lutz et al. (2022)	POS	J Clin Anesth	116	25	91	75.9	62.6	26.7	CAM-ICU, RASS	PBS
Hesse et al. (2019)	POS	Br J Anaesth	626	125	501	61.0	69.7	48.2	CAM-ICU	PBS
Koch et al. (2021)	POS	Anesth Analg	237	41	196	53.0	72.8	37.0	DSM V	DBS
Koch et al. (2023)	RCT p-h	Front Aging Neurosci	1058	198	860	54.0	69.7	47.7	DSM IV	BSR; DBS
Röhr et al. (2022)	RCT p-h	Front Aging Neurosci	1067	203	864	ND	69.7	ND	DSM IV	BSR

ROS, retrospective observational study; POS, prospective observational study; POS p-h, *post hoc* prospective observational study; RCT p-h, randomized controlled trial *post hoc*; PBS, presence of burst suppression; BSR, burst suppression ratio; DBS, duration of burst suppression (min); POD, postoperative delirium; CAM, Confusion Assessment Method; ASA, American Society of Anesthesiologists; ND, no data.

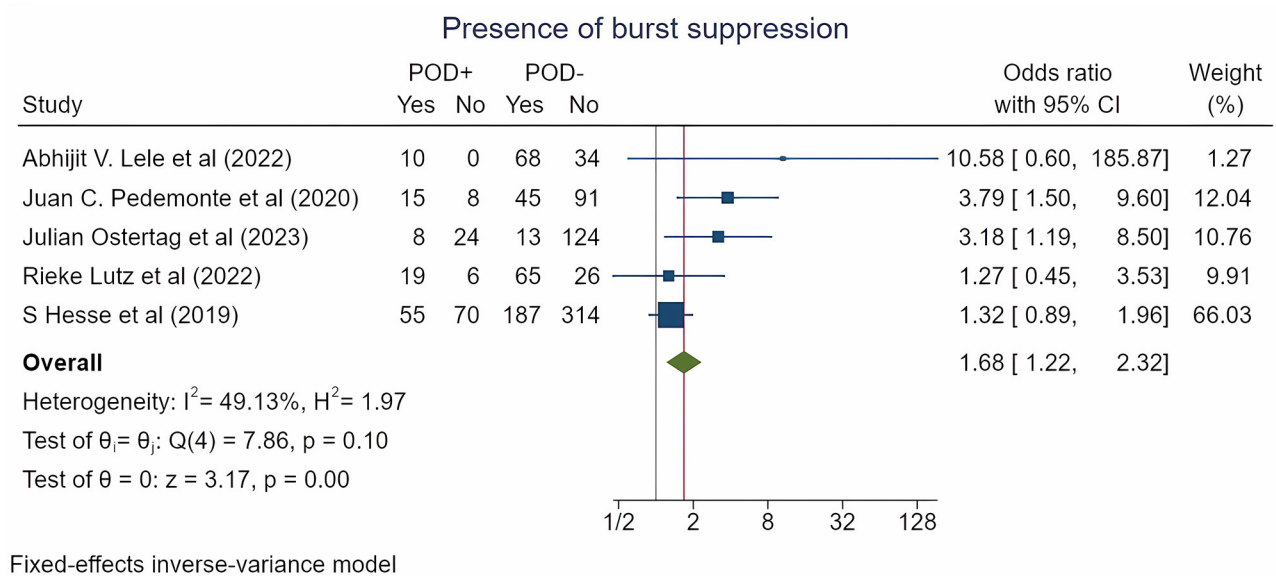

FIGURE 2
Forest plot for burst suppression incidence by POD type. The plot displays the studies, sample sizes, odds ratios, confidence intervals (CIs), and *p*-values. The size of the squares indicates the weight of the studies (considering sample size and standard deviations); the diamond represents the pooled odds ratio with CIs.

extended in patients who have developed postoperative delirium. In addition, the occurrence of a burst suppression pattern was associated with a 1.4-fold increased risk of developing POD (a relative risk increases of 41%). However, the SROC value for presence of burst suppression pattern was only 0.62, indicating that this pattern was a satisfactory prognostic factor for POD development. Investigations into other various wave patterns also demonstrated similar satisfactory predictive capabilities (the

TABLE 2 Outcomes and sensitivity analysis.

Outcome	Trials	POD+, N	POD-, N	Overall effects (95% CI)	*p*-value for overall effects	*p*-value for heterogeneity	I^2, %	*p*-value for publication bias
Burst suppression presence, *n*	5	215	967	Log OR: 0.52 (0.20; 0.84)	0.002	0.097	49.13	For log OR: 0.031
				OR: 1.68 (1.22; 2.32)	0.015	0.097	49.13	
				RR: 1.41 (1.10; 1.80)	0.006	0.021	70.04	
Duration of burst suppression, min	5	288	1280	SMD: 0.36 (0.23; 0.49)	<0.001	0.085	51.07	For SMD: 0.327
				MD: 15.86 (3.02; 28.70)	0.016	0.031	60.42	
Burst suppression ratio	2	401	1724	SMD: 0.07 (−0.04; 0.18)	0.215	0.600	0	For SMD: 0.600
				MD: 0.01 (−0.0; 0.02)	0.217	0.592	0	

POD, postoperative delirium; MD, mean difference; SMD, standardized mean difference; OR, odds ratio; Log OR, logarithm of the odds ratio; RR, risk ratio; CI, confidence interval; NA, not applicable.

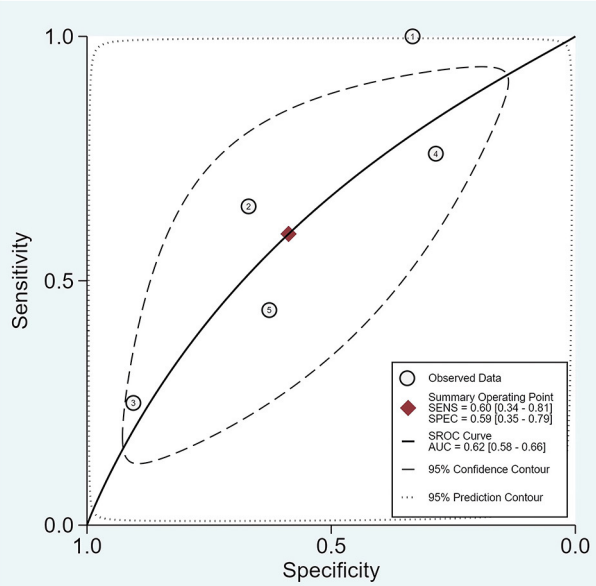

FIGURE 3
SROC for the presence of burst suppression. The plot displays the summary ROC curve (SROC) and presents AUC with 95% confidence interval (CI), 95% prediction and confidence contours, sensitivity, and specificity with CIs.

average weighted area under the curve (AUC) varied from 0.660 to 0.685).

4.2 Relationship with previous studies

This meta-analysis is the first to comprehensively examine the relationship between various EEG patterns and POD. Despite finding an association between the presence of the burst-suppression EEG pattern and the development of postoperative delirium, these results were not consistent across all studies (Hesse et al., 2019; Lele et al., 2022; Lutz et al., 2022). However, since the primary cause of this pattern is excessively deep anesthesia, our findings likely explain the results of the meta-analysis by Sumner M et al., which showed that EEG-guided anesthesia is associated with a reduced risk of POD (Sumner et al., 2023). Additionally, our results regarding the duration of burst suppression and its link to POD may also elucidate the findings of Sumner et al. (2023). In the systematic review conducted by Bruzzone et al. (2023) a detailed analysis was presented showing associations between specific intraoperative EEG parameters and the development of POD. The study found that increased magnitude and longer durations of EEG suppression, alongside a reduction in higher frequency activity, were significant indicators of POD risk. Furthermore, it was noted that an increased incidence and duration of BSR and lower BIS values are also predictive of POD development.Nonetheless, several studies have not demonstrated an association between this parameter and POD (Koch et al., 2021, 2023; Lele et al., 2022).

4.3 Significance of the study findings

The significance of our study findings can be understood in two key aspects.

First, this inaugural meta-analysis investigated the effects of deep anesthesia, characterized by the presence of a burst suppression pattern on EEG signals, on the incidence of POD. Identifying statistically significant differences in burst suppression pattern, in terms of incidence and duration, between patients with and without POD is promising for advancing our understanding of postoperative delirium prediction and prevention strategies.

Second, our meta-analysis revealed a lack of comprehensive data on intraoperative EEG patterns. A major challenge in

studying the prognostic qualities of EEG patterns is the absence of a standardized set of metrics for evaluation. This limitation hinders the possibility of conducting extensive meta-analyses. Additionally, the lack of standardization in the aspects of recording periods further diminishes the quality of the existing evidence. Despite current recommendations advocating for perioperative EEG monitoring, especially concerning the burst suppression pattern, the shift in clinical practices necessitates robust, high-quality evidence to adhere to evidence-based clinical decision-making principles. Our study provides, for the first time, high-quality evidence supporting the integration of perioperative EEG monitoring in the diagnostic framework for POD. Our results align with and reinforce the latest guidelines, thereby enhancing the evidence quality in this domain. In summary, this research not only highlights the clinical value of intraoperative EEG monitoring but also underscores the need for further high-quality studies to strengthen the evidence base in this area.

4.4 Strengths and limitations

To the best of our knowledge, this is the first meta-analysis in this field. Despite the inability to conduct a meta-analysis on a wide range of other diverse EEG patterns, we successfully grouped them based on their relation to one of the EEG waves (alpha, beta, theta, delta) and calculated the weighted average AUCs for each group. While the values of the weighted average AUCs were comparable, a more in-depth exploration of the existing patterns is of significant scientific interest. All studies included in the meta-analysis exhibited a moderate or low risk of bias, enhancing the quality of the obtained results.

Nevertheless, it is important to acknowledge the limitations in this analysis. The high heterogeneity among the studies presented in this work complicates the process of data synthesis resulting from the analysis. Additionally, the burst suppression ratio did not demonstrate statistical significance in predicting POD, which may be attributed to the limited availability of data and studies examining this pattern. We cannot overlook that the development of POD is influenced by a multitude of factors, such as patients' medical histories, characteristics of the intraoperative period, and surgical complications during the perioperative period. To gain a more precise understanding of the nature of POD onset, these factors must be considered in the analysis. We also observed significant publication bias for burst suppression incidence, which suggests that the findings should be interpreted with caution. Moreover, using EEG to predict POD during the intraoperative period has several limitations. Individual variability in brain activity, influenced by factors like age and neurological history, can complicate EEG signal interpretation. The intraoperative setting introduces artifacts from surgical and medical equipment, challenging the clarity and reliability of EEG data. Additionally, anesthetic agents alter EEG patterns, necessitating careful consideration of their effects in POD prediction. Standardization issues in EEG protocol, such as electrode placement and signal processing, further limit the consistency and generalizability of findings across studies.

4.5 Future studies and prospects

A comprehensive analysis of the conducted studies has highlighted the need for further exploration of the burst suppression pattern through the execution of high-quality prospective observational studies dedicated to its examination. The substantial heterogeneity among the studied patterns raises considerations about standardizing the methods for assessing individual types of EEG waves, potentially facilitating subsequent meta-analyses to assess the prognostic significance of these parameters in predicting postoperative delirium.

5 Conclusion

This systematic review and meta-analysis demonstrated that the occurrence of the burst suppression pattern on EEG was associated with a 41% increase in the relative risk of POD development in older patients. Additionally, the duration of burst suppression was also extended in patients with POD. Our research provides strong evidence for expanding the use of intraoperative EEG monitoring in current guidelines. This study highlights EEG's value in improving perioperative care by assessing brain activity and detecting delirium risk. Our findings advocate for integrating EEG monitoring into routine intraoperative procedures to enhance patient outcomes and support more personalized anesthetic management.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary material, further inquiries can be directed to the corresponding author.

Author contributions

VL: Conceptualization, Methodology, Project administration, Writing – original draft, Writing – review & editing. LB: Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. AS: Data curation, Investigation, Writing – original draft, Writing – review & editing. PP: Formal analysis, Methodology, Writing – original draft, Writing – review & editing. MY: Formal analysis, Writing – original draft, Writing – review & editing. NG: Data curation, Investigation, Writing – original draft, Writing – review & editing. OR: Data curation, Investigation, Writing – original draft, Writing – review & editing. IA: Writing – original draft, Writing – review & editing. MS: Project administration, Writing – original draft, Writing – review & editing. AK: Project administration, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

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References

Aldecoa, C., Bettelli, G., Bilotta, F., Sanders, R. D., Aceto, P., Audisio, R., et al. (2023). Update of the European society of anaesthesiology and intensive care medicine evidence-based and consensus-based guideline on postoperative delirium in adult patients. *Eur. J. Anaesthesiol.* 41:1876 doi: 10.1097/EJA.0000000000001876

Baron Shahaf, D., Hight, D., Kaiser, H., and Shahaf, G. (2023). Association between risk of stroke and delirium after cardiac surgery and a new electroencephalogram index of interhemispheric similarity. *J. Cardiothorac. Vasc. Anesth.* 37, 1691–1699. doi: 10.1053/j.jvca.2023.05.033

Berikashvili, L. B., Kadantseva, K. K., Ermokhina, N. V., Yadgarov, M. Y., Makarevich, D. G., Smirnova, A. V., et al. (2023). Postoperative neurocognitive disorders: the legacy of almost 400 years of history (Review). *Obs. Reanimatol.* 19, 29–42. doi: 10.15360/1813-9779-2023-4-29-42

Bruzzone, M., Walker, J., Chapin, B., Firme, M. S., Kimmet, F., Ahmed, S., et al. (2023). The role of the perioperative use of EEG as a predictor/diagnostic tool for post-operative delirium: systematic review (P10-1.008). *Neurology* 100:204149. doi: 10.1212/WNL.0000000000204149

Chew, W. Z., Teoh, W. Y., Sivanesan, N., Loh, P. S., Shariffuddin, I. I., Ti, L. K., et al. (2022). Bispectral index (BIS) monitoring and postoperative delirium in elderly patients undergoing surgery: a systematic review and meta-analysis with trial sequential analysis. *J. Cardiothorac. Vasc. Anesth.* 36, 4449–4459. doi: 10.1053/j.jvca.2022.07.004

CLARITY-group. Tool to Assess Risk of Bias in Case Control Studies Hamilton, Ontario: McMaster University (2023). Available online at: https://www.evidencepartners.com/wp-content/uploads/2021/03/Tool-to-Assess-Risk-of-Bias-in-Case-Control-Studies-DistillerSR.pdf (accessed July 14, 2023).

Dragovic, S., Schneider, G., García, P. S., Hinzmann, D., Sleigh, J., Kratzer, S., et al. (2023). Predictors of low risk for delirium during anesthesia emergence. *Anesthesiology* 139, 757–768. doi: 10.1097/ALN.0000000000004754

Dwamena, B. (2007). *MIDAS: Stata Module for Meta-Analytical Integration of Diagnostic Test Accuracy Studies. Stat. Softw. Components*, 1–2. Available online at: https://www.researchgate.net/publication/4998122_Meta-analytical_Integration_of_Diagnostic_Accuracy_Studies_in_Stata (accessed January 31, 2024).

Evered, L. A., Chan, M. T. V., Han, R., Chu, M. H. M., Cheng, B. P., Scott, D. A., et al. (2021). Anaesthetic depth and delirium after major surgery: a randomised clinical trial. *Br. J. Anaesth.* 127, 704–712. doi: 10.1016/j.bja.2021.07.021

Fritz, B. A., Kalarickal, P. L., Maybrier, H. R., Muench, M. R., Dearth, D., Chen, Y., et al. (2016). Intraoperative electroencephalogram suppression predicts postoperative delirium. *Anesth. Analg.* 122, 234–242. doi: 10.1213/ANE.0000000000000989

Guyatt, G. H., Oxman, A. D., Vist, G. E., Kunz, R., Falck-Ytter, Y., Alonso-Coello, P., et al. (2008). GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 336, 924–926. doi: 10.1136/bmj.39489.470347.AD

Hesse, S., Kreuzer, M., Hight, D., Gaskell, A., Devari, P., Singh, D., et al. (2019). Association of electroencephalogram trajectories during emergence from anaesthesia with delirium in the postanaesthesia care unit: an early sign of postoperative complications. *Br. J. Anaesth.* 122, 622–634. doi: 10.1016/j.bja.2018.09.016

Higgins, J. P. T., and Green, S. (2011). *Cochrane Handbook for Systematic Reviews of Interventions | Cochrane Training. Handbook*, 649. Available online at: https://training.cochrane.org/handbook (accessed January 31, 2024).

Higgins, J. P. T., Thomas, J., Chandler, J., Cumpston, M., Li, T., Page, M. J., et al. (2019). *Cochrane Handbook for Systematic Reviews of Interventions*. New York, NY: John Wiley and Sons.

Jung, C., Hinken, L., Fischer-Kumbruch, M., Trübenbach, D., Fielbrand, R., Schenk, I., et al. (2021). Intraoperative monitoring parameters and postoperative delirium: results of a prospective cross-sectional trial. *Med* 100:E24160. doi: 10.1097/MD.0000000000024160

Khalifa, C., Lenoir, C., Robert, A., Watremez, C., Kahn, D., Mastrobuoni, S., et al. (2023). Intra-operative electroencephalogram frontal alpha-band spectral analysis and postoperative delirium in cardiac surgery: a prospective cohort study. *Eur. J. Anaesthesiol.* 40, 777–787. doi: 10.1097/EJA.0000000000001895

Kinoshita, H., Saito, J., Kushikata, T., Oyama, T., Takekawa, D., Hashiba, E., et al. (2023). The perioperative frontal relative ratio of the alpha power of electroencephalography for predicting postoperative delirium after highly invasive surgery: a prospective observational study. *Anesth. Analg.* 137, 1279–1288. doi: 10.1213/ANE.0000000000006424

Koch, S., Blankertz, B., Windmann, V., Spies, C., Radtke, F. M., and Röhr, V. (2023). Desflurane is risk factor for postoperative delirium in older patients' independent from intraoperative burst suppression duration. *Front. Aging Neurosci.* 15:1067268 doi: 10.3389/fnagi.2023.1067268

Koch, S., Windmann, V., Chakravarty, S., Kruppa, J., Yürek, F., Brown, E. N., et al. (2021). Perioperative electroencephalogram spectral dynamics related to postoperative delirium in older patients. *Anesth. Analg.* 133, 1598–1607. doi: 10.1213/ANE.0000000000005668

Lele, A. V., Furman, M., Myers, J., Kinney, G., Sharma, D., and Hecker, J. (2022). Inadvertent burst suppression during total intravenous anesthesia in 112 consecutive patients undergoing spinal instrumentation surgery: a retrospective observational quality improvement project. *J. Neurosurg. Anesthesiol.* 34, 300–305. doi: 10.1097/ANA.0000000000000754

Li, N., Liu, X., Gao, Y., Yin, L., Zhao, W., Ma, R., et al. (2022). Association of electroencephalogram epileptiform discharges during cardiac surgery with postoperative delirium: an observational study. *Front. Surg.* 9:900122. doi: 10.3389/fsurg.2022.900122

Liberati, A., Altman, D. G., Tetzlaff, J., Mulrow, C., Gøtzsche, P. C., Ioannidis, J. P. A., et al. (2009). The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J. Clin. Epidemiol.* 62, e1–e34. doi: 10.1016/j.jclinepi.2009.06.006

Literature Map Software for Lit Reviews and Research and Litmaps (2024). Available online at: https://www.litmaps.com/ (accessed January 31, 2024).

Luo, D., Wan, X., Liu, J., and Tong, T. (2018). Optimally estimating the sample mean from the sample size, median, mid-range, and/or mid-quartile range. *Stat. Methods Med. Res.* 27, 1785–1805. doi: 10.1177/0962280216669183

Lutz, R., Müller, C., Dragovic, S., Schneider, F., Ribbe, K., Anders, M., et al. (2022). The absence of dominant alpha-oscillatory EEG activity during emergence from delta-dominant anesthesia predicts neurocognitive impairment- results from a prospective observational trial. *J. Clin. Anesth.* 82:110949 doi: 10.1016/j.jclinane.2022.110949

McGuinness, L. A., and Higgins, J. P. T. (2021). Risk-of-bias VISualization (robvis): an R package and Shiny web app for visualizing risk-of-bias assessments. *Res. Synth. Methods* 12, 55–61. doi: 10.1002/jrsm.1411

Momeni, M., Meyer, S., Docquier, M. A., Lemaire, G., Kahn, D., Khalifa, C., et al. (2019). Predicting postoperative delirium and postoperative cognitive decline with combined intraoperative electroencephalogram monitoring and cerebral near-infrared spectroscopy in patients undergoing cardiac interventions. *J. Clin. Monit. Comput.* 33, 999–1009. doi: 10.1007/s10877-019-00253-8

O'Regan, N. A., Fitzgerald, J., Timmons, S., O'Connell, H., and Meagher, D. (2013). Delirium: a key challenge for perioperative care. *Int. J. Surg.* 11, 136–144. doi: 10.1016/j.ijsu.2012.12.015

Ostertag, J., Engelhard, A., Nuttall, R., Aydin, D., Schneider, G., García, P. S., et al. (2024). Development of postanesthesia care unit delirium is associated with differences in aperiodic and periodic alpha parameters of the electroencephalogram during emergence from general anesthesia: results from a prospective observational cohort study. *Anesthesiology* 140, 73–84. doi: 10.1097/ALN.0000000000004797

Pedemonte, J. C., Plummer, G. S., Chamadia, S., Locascio, J. J., Hahm, E., Ethridge, B., et al. (2020). Electroencephalogram burst-suppression during cardiopulmonary bypass in elderly patients mediates postoperative delirium. *Anesthesiology* 133, 280–292. doi: 10.1097/ALN.0000000000003328

Reese, M., Christensen, S., Anolick, H., Roberts, K. C., Wong, M. K., Wright, M. C., et al. (2023). EEG pre-burst suppression: characterization and inverse association with preoperative cognitive function in older adults. *Front. Aging Neurosci.* 15:1229081. doi: 10.3389/fnagi.2023.1229081

Rohatgi, A. (2010). *WebPlotDigitizer - Extract Data From Plots, Images, and Maps. Arohatgi*. Available online at: http://arohatgi.info/WebPlotDigitizer/ (accessed January 31, 2024).

Röhr, V., Blankertz, B., Radtke, F. M., Spies, C., and Koch, S. (2022). Machine-learning model predicting postoperative delirium in older patients using intraoperative frontal electroencephalographic signatures. *Front. Aging Neurosci.* 14:911088. doi: 10.3389/fnagi.2022.911088

Soehle, M., Dittmann, A., Ellerkmann, R. K., Baumgarten, G., Putensen, C., and Guenther, U. (2015). Intraoperative burst suppression is associated with postoperative delirium following cardiac surgery: A prospective, observational study. *BMC Anesthesiol.* 15:51. doi: 10.1186/s12871-015-0051-7

Sumner, M., Deng, C., Evered, L., Frampton, C., Leslie, K., Short, T., et al. (2023). Processed electroencephalography-guided general anaesthesia to reduce postoperative delirium: a systematic review and meta-analysis. *Br. J. Anaesth.* 130, e243–e253. doi: 10.1016/j.bja.2022.01.006

Sun, Y., Wei, C., Cui, V., Xiu, M., and Wu, A. (2020). Electroencephalography: clinical applications during the perioperative period. *Front. Med.* 7:251. doi: 10.3389/fmed.2020.00251

Wan, X., Wang, W., Liu, J., and Tong, T. (2014). Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med. Res. Methodol.* 14, 1–13. doi: 10.1186/1471-2288-14-135

Windmann, V., Dreier, J. P., Major, S., Spies, C., Lachmann, G., and Koch, S. (2022). Increased direct current-electroencephalography shifts during induction of anesthesia in elderly patients developing postoperative delirium. *Front. Aging Neurosci.* 14:921139. doi: 10.3389/fnagi.2022.921139

World Health Organisation (1994). *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines, Tenth Revision. Null Null, Null.* Available online at: https://iris.who.int/bitstream/10665/246208/1/9789241549165-V1-eng.pdf (accessed February 3, 2024).

Yan, E., Veitch, M., Saripella, A., Alhamdah, Y., Butris, N., Tang-Wai, D. F., et al. (2023). Association between postoperative delirium and adverse outcomes in older surgical patients: a systematic review and meta-analysis. *J. Clin. Anesth.* 90:111221 doi: 10.1016/j.jclinane.2023.111221

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The 4AT scale for rapid detection of delirium in emergency department triage

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Aims: To assess the diagnostic accuracy and time impact of the 4AT scale in emergency department triage.

Methods: A Prospective diagnostic accuracy study was carried out. People aged ≥65 years presenting to the emergency department from 1 November 2021 to 30 June 2022 were included. Nurses opportunistically screened eligible patients using the 4AT scale during triage according to the Manchester Triage System Francesc de Borja Hospital emergency department, Gandía (Spain). Accuracy was compared with medical diagnosis of delirium. Time (seconds) spent in triage with and without screening was assessed.

Results: The study included 370 patients (55.1% men, mean age 81.8 years), of whom 58.4% (n = 216) were screened. A final diagnosis of delirium was made in 41.4% of those screened. The most frequently used presentational flow charts and discriminators were 'behaving strangely' (15%) and 'rapid onset' (33.3%). The highest accuracy was obtained for a score of 3 points or more (sensitivity 85.1%; specificity 66.9%; positive predictive value 52.8%; negative predictive value 71.7%). No significant differences were found in the time spent in triage according to the performance of screening.

Conclusion: A score of 3 points or more on the 4AT scale enables rapid detection of delirium in emergency department triage, without consuming more time than conventional triage.

KEYWORDS

delirium, aged, emergency service hospital, triage, data accuracy

1 Introduction

Delirium is an acute neurobehavioral syndrome, characterized by acute and fluctuating disturbances of consciousness and attention in addition to possible disorientation, hallucinations, restlessness, confusion, and inappropriate behavior in hyperactive subtype or lethargy or increased sleepiness in hypoactive subtype (1). Research and clinical practice demonstrated that the development of delirium is multifactorial and involves a complex interrelationship between patient-, healthcare-and pharmacotherapy-related factors. The multifactorial nature is due to the concurrence of predisposing factors and precipitating factors. Age, cognitive deficit, drugs, sensory deficits, comorbidity and dehydration are some

predisposing factors and urinary and respiratory infections and the administration or deprivation of psychotropic drugs and the administration of anticholinergic drugs as precipitating factors, as well as harsh hospital techniques (2). The syndrome has significant consequences for both the patient and the healthcare system, including higher rates of functional dependency and longer hospital stays, as well as increased risk of falling, institutionalization, morbidity, and mortality (3). Indeed, people with delirium carry almost three times the risk of death after hospital admission and at 6 months follow-up than those without (4–6).

Among older adults presenting to the emergency department (ED), an estimated 7 to 20% have delirium (1, 7, 8) with prevalence rising to 89% in people with pre-existing cognitive dysfunction or dementia (9). However the fluctuating nature of delirium results in under-diagnosis and under-treatment, with up to 83% cases being missed (3, 10).

There is a need to prioritize urgent care for all patients attending to ED. Triage is a method used to assess the severity of the patient's condition and determine the level of priority for ED care. The nurse team is usually the responsible for this assessment. Every individual arriving at the ED requires an initial assessment, triage, which is conducted by the nursing team to determine and prioritize their care needs. The Manchester Triage System (MTS) is a systematized protocol to determine the patient's severity as well as associated risks and needs, according to the flow chart, thus optimizing waiting time and resource use according to care needs (11). This process aims to provide a rapid and dynamic assessment (2, 12). Accurate and early detection of delirium may provide opportunities for identifying high-risk patients, potentially preventing or minimizing cases of delirium in the ED (9, 10, 13).

There are short, validated cognitive screening tools that could enable early identification of vulnerable older people, triggering appropriate care pathways and urgent assessment of people with possible delirium (4, 14). The most tools used are the 4 "A's Test (4AT), Confusion Assessment Method (CAM), Confusion Assessment Method for the Intensive Care Unit (CAM-ICU), Brief Confusion Assessment Method (bCAM), 3-Minute Diagnostic Confusion Assessment Method (3D-CAM) and, Spatial Span Forwards (SSF), Clock Drawing Test (CDT) and Delirium Triage Screen (DTS). The common characteristic is that they are quick screening scales, generally requiring less than 3 min, suitable to be performed in the ED (15). Early detection and intervention in people with delirium is a strong indicator of the quality of hospital care for vulnerable patients (16, 17). Thus, this study aims to assess the accuracy of the 4AT scale, as administered by ED nurses in triage, and to compare time spent in triage between participants screened with the 4AT and those not screened.

2 Methods

2.1 Study design, setting and participants

This prospective diagnostic accuracy study included people aged 65 years or older who went to the ED between 1 November 2021 and 30 June 2022. Based on the findings of previous research the older persons with the highest risk of presenting delirium in ED were those with predisposing and precipitating factors such as dementia, previous stroke and infections or sedative drugs, respectively, in the triage assessment (18). In addition to patients who, after triage assessment following the MTS method by the nursing professional, are classified by flow charts 'unwell adult' or 'abnormal behavior', and/or discriminators 'sudden onset' or 'a new neurological deficit less than 24 h old' (11).

So, eligible patients presented predisposing and precipitating risk factors for delirium during triage by nursing professionals, (18) or were evaluated using the 'unwell adult' or 'behaving strangely' MTS flow charts with 'rapid onset' and 'new neurological deficit less than 24 h old' discriminators. The cognitive status of the patient with delirium is almost always compromised, so in such cases, the informed consent was signed by the family members of the participants. Participants who did not have family members to complete the informed consent form or decided not to take part in the study were excluded, as were people with delirium tremens or drug or substance intoxication.

All patients were seen in the ED at the Hospital Francesc de Borja de Gandía, Spain. This is a secondary, 256-bed, academic hospital with a catchment population of 188,000 and an average annual volume of 60,000 admitted ED encounters. The ED service is organized into eight care areas. In addition to the triage and admissions areas, the ED service has six care areas: consultations, resuscitation, observation, pediatrics, traumatology, and treatment room. Triage is performed by the nursing staff 24 h a day, 7 days a week. The ED is staffed by nine nurses during the morning and afternoon shifts, and seven nurses on the night shift. At least one nurse on each shift is responsible for triaging patients who come to the ED after being registered for emergency admission.

2.2 Sample size

A total of 8,426 people over 65 years of age attended the emergency department between November 1, 2021 and June 2, 2022. For a confidence level of 95% and a margin of error of 5%, a sample size of 368 participants was calculated.

2.3 Procedures

In 2011, the Edinburgh Delirium Research Group (Scotland, UK) developed the 4AT delirium screening scale, which consists of four items: an assessment of the level of alertness, an orientation test, an attention test, and finally an item determining acute change or fluctuating course (19). The instrument has since been translated to different languages and validated in multiple clinical settings, including the ED (20). The 4AT was used at first patient contact to rule out suspected delirium. It is an optimal tool for the ED because the estimated time for evaluation is <2 min. The Sensitivity is 89.7% and the specificity is 84.1% (21).

Following recruitment of the study cohort, participating nursing professionals opportunistically performed delirium screenings using the 4AT scale in the triage area, during all 7 days of the week and all three work shifts. Administration of the screening tool was contingent on having a sufficient number of professionals per shift, a manageable care load, and an acceptable time delay to receive health care.

The results of the 4AT screening were added to each patient's medical record as supplementary information for physicians. The diagnostic process was based on the DSM-V criteria, which include alteration of attention and consciousness, development over a short

period of time, and additional changes in cognition and attention that are not attributable to a preexisting or developing neurocognitive disorder, or to a state of severe consciousness impairment (coma). Additionally, the 4AT score and the results of complementary tests were used to establish the patient's final diagnosis, determining whether it was delirium or another condition. Following care, follow-up and diagnosis, the group screened with the 4AT scale were classified according to whether they received a medical diagnosis of delirium following DSM-V criteria (Screened with 4AT and Delirium Yes): disturbance in attention and awareness; develops over a short period of time; and additional disturbance in cognition, attention and cognition are not from a pre-existing or evolving neurocognitive disorder or from severely reduced arousal (coma) and those who were diagnosed with other pathology (Screened with 4AT and Delirium No). We also identified eligible patients who were not screened with the 4AT scale but were diagnosed with delirium (Not screened with 4AT and Delirium Yes), along with patients who fit selection criteria but did not have delirium, collecting data from their medical records following the ED episode (Not screened with 4AT and Delirium No) (Figure 1).

2.4 Data collection

In addition to collecting the results of the 4AT scale and the medical diagnosis using the ICD-10 code, we recorded sociodemographic data (age, sex) and comorbidities related to delirium (dementia, incontinence, history of stroke, and fall in the previous 30 days). Additionally, MTS variables were the presentational flow chart, discriminator, and priority, as well as the time spent by nurses in triage and the waiting time to be seen by the physician. Finally, the length of hospital stay in case of admission was collected.

2.5 Ethical considerations

The Hospital Francesc de Borja ethics committee approved the study. Patient confidentiality was preserved in line with Spanish legislation on the protection of personal data following Organic Law 3/2018, of 5 December, on Protection of Personal Data and Guarantee of Digital Rights. The study was carried out in accordance with the principles of the Declaration of Helsinki. All participants signed informed consent.

2.6 Statistical analysis

All data entered into the database were verified by an independent second person. Descriptive statistics were expressed as mean and standard deviation (SD) for normally distributed continuous variables and relative frequencies for categorical (qualitative) variables.

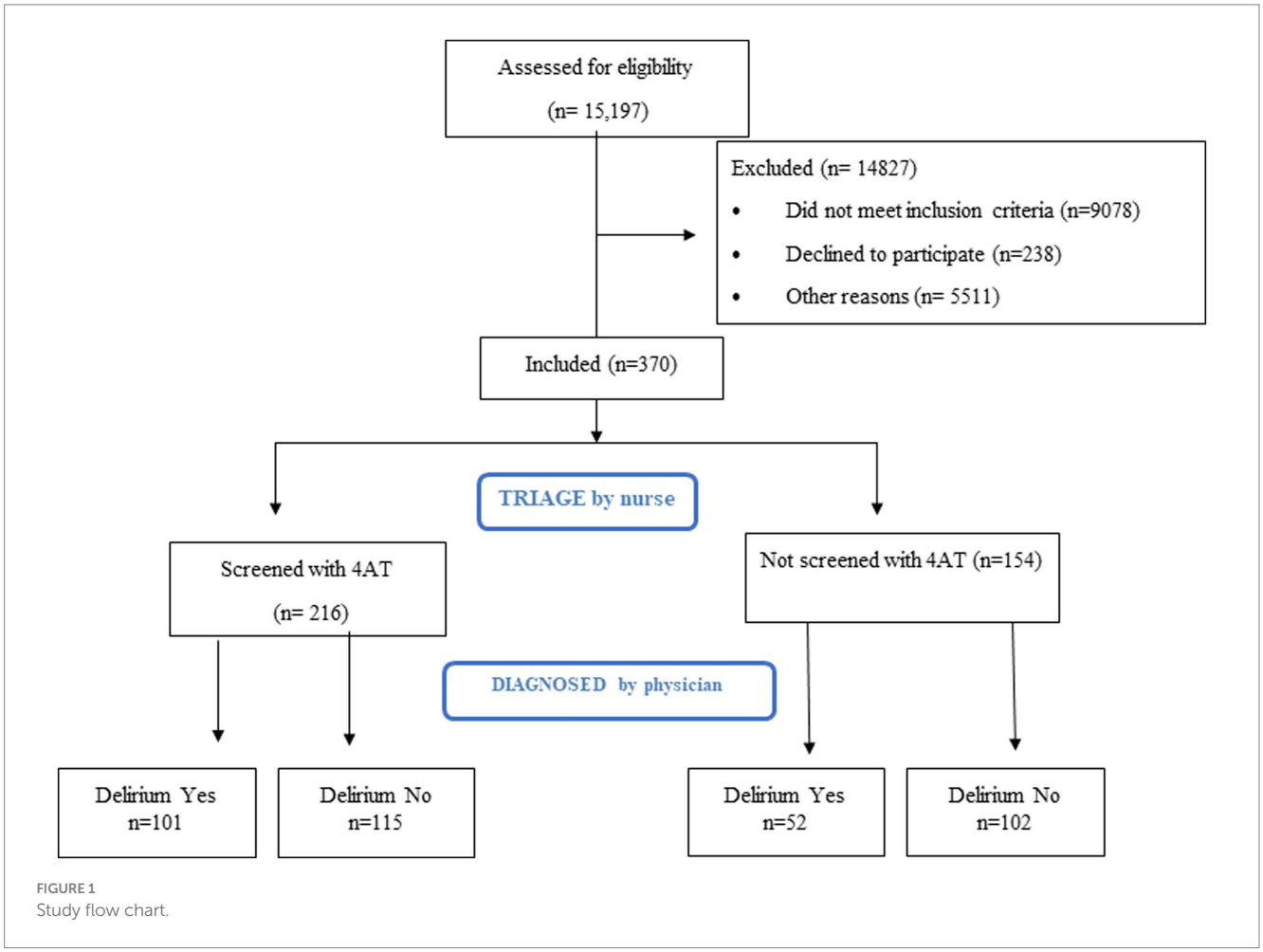

FIGURE 1
Study flow chart.

The risk of delirium according to comorbidities was quantified using the crude odds ratio (OR). The accuracy of the 4AT scale for diagnosing delirium was assessed according to the scale validation cutoff (≥4 points), using the medical diagnosis based on DSM-V criteria as a gold standard. In addition, the receiver operating characteristics (ROC) curve was used to determine the cutoff value and sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of 4AT scores and delirium.

Data were entered in MS Excel spreadsheets, then imported for analysis to SPSS (version 28.0, IBM Corp. Released 2015. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp).

3 Results

During the recruitment period, 53,110 patients were seen in the ED of the study center: 28.6% ($n = 15,197$) were aged 65 years or over, and 216 of these were screened with the 4AT scale by the triage nurses. Another group of 154 patients were included in the study because they met selection criteria but were not screened using the 4AT scale to analyse the accuracy of de 4AT.

Thus, a total of 370 participants were assessed: 41.4% ($n = 153$) were coded with a diagnosis of delirium according to the ICD-10, while the remaining 58.6% ($n = 217$) finally received a different diagnosis.

The sample was predominantly male, and participants' mean age was 81.82 years, with significant differences between those diagnosed with delirium versus those who were not (84.04 years versus 80.25 years; mean difference [MD] 3.79, 95 confidence interval [CI] 2.14–5.43, $p < 0.001$). On the other hand, there were no significant differences between groups according to sex or priority (Table 1).

Regarding the MTC flow charts and discriminators, patients with a diagnosis of delirium were more likely to be assessed using the 'behaving strangely' (15%) flow chart with the 'rapid onset' (33.3%) discriminator than the sample as a whole. Regarding comorbidities, people with dementia had nearly three times the odds of having delirium (OR 2.6, 95% CI 1.58, 4.26, $p < 0.001$).

According to the 4AT tool, 84 (38.9%) of the 216 patients had a positive screening result for delirium, while 101 (46.8%) received a medical diagnosis according to DSM-V criteria.

Table 2 shows the accuracy indicators for the 4AT screening test. For the cutoff point proposed in the validation study, the highest sensitivity (94.3%) and specificity (92.0%) were observed in people with dementia. In contrast, these values were lower in older people without dementia and therefore in the screened population as a whole.

We analyzed which cutoff point presented the highest diagnostic accuracy for the total sample, observing that a score of 3 points or more on the 4AT scale has the best sensitivity in older people without dementia (82.3%) and therefore in the overall sample (85.1%) (Table 2).

Finally, we quantified the time spent performing triage (Figure 2A). The duration of the triage encounters with 4AT screening (mean 218 s SD 104) was similar to triage without screening (mean 213 s SD 113). The scant 5 additional seconds it took to perform screening did not constitute a significant difference (MD 5 95% CI −17, 27; $p = 0.665$).

The average length of hospital stay in participants screened with the 4AT scale episode was half that of patients not screened (mean 6.9 days SD 6.9 vs. 13.3 days SD 44.0, MD 6.4 days; 95% CI −16.9, 4.1; $p = 0.23$), although this difference was not significant (Figure 2B).

4 Discussion

Detecting delirium in older people remains a challenge in the ED due to the atypical presentation of many diseases in this population, the existence of several types of delirium, and the failure to implement standardized detection tools in triage settings, despite their availability (22). This research focuses on the detection of delirium in the ED setting in order to improve quality of care in older patients with or at risk of this syndrome. The aim of our study was to determine the accuracy of the 4AT scale performed by nurses in ED triage and to assess the extra time needed for screening in the triage setting. We found that a score of 3 or more points on the 4AT scale accurately identifies people with delirium in ED triage without requiring more time than that spent in conventional triage.

Most studies that analyze delirium in older persons in ED obtain samples of lower age and with a higher percentage of women than those found in our sample. A higher mean age could explain the higher incidence found in the present study. The incidence was 41.4%, which is higher than the 7 to 35% reported elsewhere (7, 18). Within the range of people over 65 years of age or more, older people of 80 years or more present a higher risk of delirium. This aspect is related to the changes inherent to the aging process and to the fact that older people generally have more comorbidity and a greater number of predisposing risk factors. Older age increases almost 3 fold the risk of suffering from delirium with respect to younger older people (23). Indeed, our results showed a higher proportion of males but in pooled analyses the literature does not show a direct association by sex. Finally, the active search through delirium screening for people at higher risk of suffering from delirium could also justify the high prevalence in the population analyzed (24).

The MTS system is a formalized initial assessment system whose main objective is to optimize the waiting time for the first ED assessment by prioritizing acute life-threatening cases (25). Our analysis of MTS is consistent with recent studies showing that priority 3 (urgent) (26) is the priority par excellence assigned to patients with delirium. Regarding the flow chart and discriminators, the most commonly used are 'unwell adult' and 'behaving strangely' (11). Although this system is general and does not cover all presentation characteristics, recent studies have even shown that it is inadequate as a predictor of severity and mortality (27) especially in older people. More research is needed in this area because nurses with specific knowledge for proper triage (28). Can perform an adequate assessment for the older since the presentation of pathologies may differ with respect to younger populations due to changes in the aging process (12, 29).

The implementation of validated tools specific to older people in the ED setting would improve early detection and minimize the time to optimal treatment (30). The 4AT was specifically designed for routine clinical use in 2011. The Edinburgh Delirium Research Group determined a cutoff of 4 or more points for delirium, and the tool was validated using this cutoff in 2014 (21). However, our results indicate that the 4-point cutoff proposed by the authors presents greater accuracy in people with dementia, while the 3-point cutoff shows greater sensitivity and specificity for the general population of older people (19).

Several meta-analyses have identified greater sensitivity and specificity in the 4AT scale in the older population in the same setting than that obtained in our study (31, 32). However, the age of the

TABLE 1 Sociodemographic profile and Manchester triage variables.

	Delirium (*N* = 153)	No Delirium (*N* = 217)	Total (*N* = 370)	
	n (%)*	*n* (%)*	*n* (%)*	*p* value†
Age, years, mean (SD)	84.04 (7.68)	80.25 (8.11)	81.82 (8.14)	<0.001
Sex				
Male	77 (50.3)	127 (58.5)	204 (55.1)	0.12
Female	76 (49.7)	90 (41.5)	166 (44.9)	
Priority				
Level 2 (orange)	10 (6.5)	16 (7.4)	26 (7.0)	0.74
Level 3 (yellow)	95 (62.1)	126 (58.1)	221 (59.7)	
Level 4 (green)	48 (31.4)	74 (34.1)	122 (33.0)	
Level 5 (blue)	0 (0)	1 (0.5)	1 (0.3)	
MTC flow chart				
Unwell adult	84 (54.9)	125 (57.6)	209 (56.5)	0.002
Behaving strangely	23 (15.0)	11 (5.1)	34 (9.2)	
Others	46 (30.1)	81 (37.3)	127 (34.3)	
MTC Discriminators				
Rapid onset	51 (33.3)	69 (31.8)	120 (32.4)	0.41
Recent issue	23 (15.0)	34 (15.7)	57 (15.4)	
New neurological deficit (< 24 h)	12 (7.8)	7 (3.2)	19 (5.1)	
Others	67 (43.8)	107 (49.3)	174 (47.0)	
Comorbidities				
Dementia	51 (33.3)	35 (16.1)	86 (23.2)	<0.001
Previous stroke	22 (14.4)	17 (7.8)	39 (10.5)	0.043
Falls in the last 30 days	31 (20.3)	31 (14.3)	62 (16.8)	0.13
Incontinence	48 (31.1)	50 (23.0)	98 (26.5)	0.074
Diabetes	48 (31.4)	66 (30.4)	114 (30.8)	0.84
4AT	(N = 101)	(N = 115)	(N = 216)	
4AT scores, mean (SD)	5.8 (3.51)	4.97 (2.89)	5.36 (3.26)	0.056
4AT ≥4	70 (69.31)	67 (58.26)	137 (58.79)	0.093

MTS, Manchester Triage System. *Unless otherwise noted. †Quantitative variables compared using student's *t* test; categorical variables using the Chi² test.

samples and the incidence was generally lower than that found in our results, which may be influenced by comorbidity, the presence of cognitive impairment or the cause of delirium. Efforts have been made to determine the most appropriate tool for the detection of delirium in ED, since the CAM scale and the 3D CAM scale are the most widely used and have very good diagnostic accuracy. In ED the need for speed in the assessment both for obtaining the results and for the least time investment should also be an essential aspect to take into account in the assessment procedures, for this reason the 4AT scale is being proposed as the most suitable for the ED setting, (31, 32) even for the detection of cognitive impairment (32). The possible use of different cutoff points increases diagnostic accuracy and therefore detection, so there is a need for studies to analyse different populations and cutoffs, which would help to increase detection through the consideration of comorbidity (20). In addition to designing studies with high methodological quality for greater validity of the results (32).

Finally, some studies suggest that longer hospital stays have short-and long-term effects in patients with delirium (33). The 4AT scale is useful for detecting delirium in the ED, does not require specific training to administer, and requires only about 2 min to perform (19, 32). In our study, the time spent on triage with versus without delirium screening was compared, and no differences were found, with an average of only 5 s more time spent in triage that included screening. These data demonstrate that screening does not interfere in the ED prioritization process (32).

The results obtained on the 4AT scale provide further information to the physician. The teamwork model within the ED makes it difficult to know at what time the physician diagnoses delirium and at what exact moment a treatment is administered by the nursing professional once he/she reads and executes the physician's order. If the physician has the result of the 4AT scale screening when the physician performs the assessment, he has more information and could perform a faster assessment and therefore prescribe a treatment in less time, which would mean that the nursing professional could administer the treatment earlier. The literature states that early detection enables prompt diagnosis and treatment, and this is associated with shorter and less severe episodes of delirium (34). The mean length of hospital

TABLE 2 Diagnostic accuracy of the 4AT scale according to two cutoffs, compared to gold standard medical diagnosis using DSM-V criteria in patients with and without dementia.

	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	Youden Index
4AT Cut off ≥ 4					
Total ($n = 216$)	69.3 (78.3, 60.3)	41.7 (50.7, 32.7)	59.3 (68.9, 49.7)	68.4 (76.9, 59.9)	0.11
Dementia ($n = 64$)	94.3 (101.9, 86.6)	92.0 (102.6, 81.4)	58.9 (75.2, 42.6)	25.0 (42.0, 8.0)	0.86
No dementia ($n = 152$)	59.7 (71.9, 47.5)	48.9 (59.2, 38.6)	45.7 (58.1, 33.3)	64.8 (74.7, 54.9)	0.09
4AT Cut off ≥ *3*					
Total ($n = 216$)	85.1 (92.1, 78.2)	66.9 (75.5, 58.3)	52.8 (62.5, 43.2)	71.7 (79.9, 63.5)	0.52
Dementia ($n = 64$)	89.7 (99.3, 80.2)	100	58.3 (73.8, 42.9)	0	0.90
No dementia ($n = 152$)	82.3 (91.8, 72.7)	57.8 (68.0, 47.6)	49.5 (62.0, 37.1)	77.5 (86.13, 68.87)	0.40

CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value.

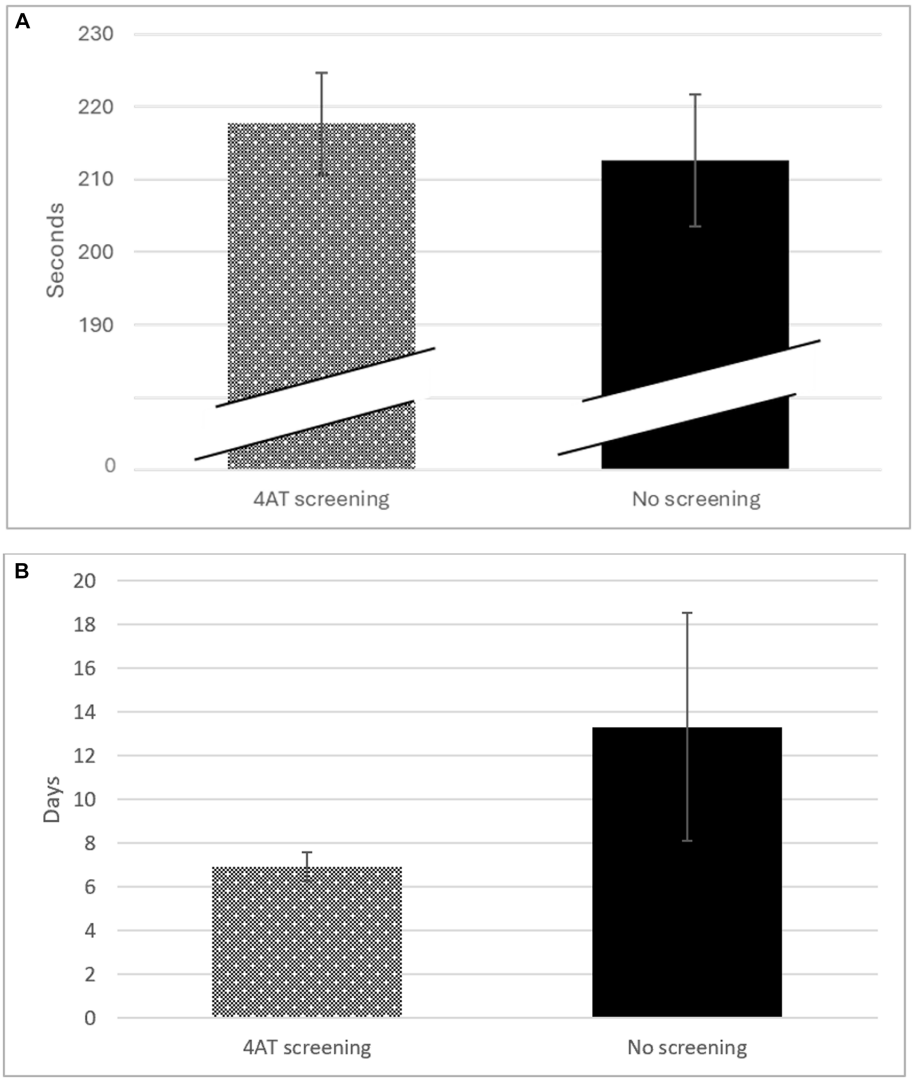

FIGURE 2
(A) Time (Seconds) spent in triage according to performance of screening with the 4AT scale. **(B)** Length of hospital stay according to the performance of screening with the 4AT scale.

stay following the ED episode was shorter in participants screened with the 4AT scale than in patients who did not undergo screening (6.9 SD 8.9 days vs. 13.3 SD 44.0 days). Evidence suggests that screening reduces the length of hospital stay by 2 days in people diagnosed with delirium (24). Data from our study are highly relevant, because length of stay was half that in patients who were screened

versus those who were not. The improvement in hospitalization data could be to considering both the urgency determined by a triage tool and the results of geriatric screening (35). These data are an important advance for clinical care and researchers, particularly where optimized care could prevent the development of delirium and minimize its causes.

4.1 Limitations

The impossibility of administering the 4AT scale in patients with reduced awareness, communication barriers, or the absence of a family member as exclusion criteria has reduced the possible size of the final sample. The time from the start of the emergency episode to the start of treatment was not analyzed, as there is no electronic record of this action. Likewise, it was not possible to assess the severity of delirium.

4.2 Strengths

In daily clinical practice, delirium screening by nursing staff in older persons at risk of delirium presenting to the ED can assist the physicians in diagnosing delirium without significant increase in time. In addition, it could aid in early detection and treatment, which could prevent further severity, prolonged hospital stays and worse outcomes. The need for longitudinal studies to understand the whole process implies that future studies should address early detection, possible biomarkers and their relationship to severity and consequences.

5 Conclusion

The 4AT scale is an accurate screening tool for delirium in older people in the ED. A score of 3 points or more allows people with delirium to be identified in ED triage without consuming more time than that spent in conventional triage. The use of the combined Manchester triage tool, together with the validated 4AT screening, helps to categorize the need for urgent care and shorten hospital admissions.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Hospital Francesc de Borja Ethics committee. The studies were conducted in accordance with the local legislation and institutional requirements. Written informed consent for participation in this study was provided by the participants' legal guardians/next of kin.

Author contributions

AS-S: Data curation, Formal analysis, Investigation, Writing – original draft. FM-A: Conceptualization, Formal analysis, Writing – review & editing. JS-F: Writing – review & editing. PP-R: Conceptualization, Formal analysis, Funding acquisition, Supervision, Writing – original draft, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

References

1. El Hussein MT, Hirst S, Stares R. Delirium in emergency departments: is it recognized? *J Emerg Nurs*. (2021) 47:809–17. doi: 10.1016/j.jen.2021.01.009

2. Raso J, Santos LMC, Reis DA, Frangiotti MAC, Zanetti ACB, Capucho HC, et al. Hospitalizations of older people in an emergency department related to potential medication-induced hyperactive delirium: a cross-sectional study. *Int J Clin Pharm*. (2022) 44:548–56. doi: 10.1007/s11096-022-01378-8

3. Béland E, Nadeau A, Carmichael P-H, Boucher V, Voyer P, Pelletier M, et al. Predictors of delirium in older patients at the emergency department: a prospective multicentre derivation study. *CJEM*. (2021) 23:330–6. doi: 10.1007/s43678-020-00004-8

4. Lee S, Okoro UE, Bobb Swanson M, Mohr NM, Faine B, Carnahan R. 197 the use of high-risk medications in the emergency department and the prevalent delirium within the first 24 hours of hospitalization. *Ann Emerg Med*. (2020) 76:S76. doi: 10.1016/j.annemergmed.2020.09.209

5. Aung Thein MZ, Pereira JV, Nitchingham A, Caplan GA. A call to action for delirium research: Meta-analysis and regression of delirium associated mortality. *BMC Geriatr*. (2020) 20:325. doi: 10.1186/s12877-020-01723-4

6. Abelha FJ, Luís C, Veiga D, Parente D, Fernandes V, Santos P, et al. Outcome and quality of life in patients with postoperative delirium during an ICU stay following major surgery. *Crit Care*. (2013) 17:R257. doi: 10.1186/cc13084

7. Hasemann W, Grossmann FF, Stadler R, Bingisser R, Breil D, Hafner M, et al. Screening and detection of delirium in older ED patients: performance of the modified confusion assessment method for the emergency department (mCAM-ED). A two-step tool. *Intern Emerg Med*. (2018) 13:915–22. doi: 10.1007/s11739-017-1781-y

8. Stanich JA, Silva LOJE, Ginsburg AD, Mullan AF, Jeffery MM, Bellolio F. Increased short-term mortality among patients presenting with altered mental status to the emergency department: a cohort study. *Am J Emerg Med*. (2022) 51:290–5. doi: 10.1016/j.ajem.2021.10.034

9. Morandi A, Inzitari M, Udina C, Gual N, Mota M, Tassistro E, et al. Visual and hearing impairment are associated with delirium in hospitalized patients: results of a multisite prevalence study. *J Am Med Dir Assoc*. (2021) 22:1162–1167.e3. doi: 10.1016/j.jamda.2020.09.032

10. Silva LOJE, Stanich JA, Jeffery MM, Lindroth HL, Miller DM, Campbell RL. Association between emergency department modifiable risk factors and subsequent delirium among hospitalized older adults. *Am J Emerg Med*. (2022) 53:201–7. doi: 10.1016/j.ajem.2021.12.032

11. Soler-Sanchis A, Martínez-Arnau FM, Sánchez-Frutos J, Pérez-Ros P. Identification through the Manchester triage system of the older population at risk of delirium: a case-control study. *J Clin Nurs*. (2022) 32:2642–51. doi: 10.1111/jocn.16349

12. Ausserhofer D, Zaboli A, Pfeifer N, Solazzo P, Magnarelli G, Marsoner T, et al. Errors in nurse-led triage: an observational study. *Int J Nurs Stud*. (2021) 113:103788. doi: 10.1016/j.ijnurstu.2020.103788

13. Mansutti I, Saiani L, Palese A. Detecting delirium in patients with acute stroke: a systematic review of test accuracy. *BMC Neurol*. (2019) 19:310. doi: 10.1186/s12883-019-1547-4

14. O'Sullivan D, Brady N, Manning E, O'Shea E, O'Grady S, O'Regan N, et al. Validation of the 6-item cognitive impairment test and the 4AT test for combined delirium and dementia screening in older emergency department attendees. *Age Ageing*. (2018) 47:61–8. doi: 10.1093/ageing/afx149

15. Saviano A, Zanza C, Longhitano Y, Ojetti V, Franceschi F, Bellou A, et al. Current trends for delirium screening within the emergency department. *Medicina*. (2023) 59:1634. doi: 10.3390/medicina59091634

16. Arbabi M, Ziaei E, Amini B, Ghadimi H, Rashidi F, Shohanizad N, et al. Delirium risk factors in hospitalized patient: a comprehensive evaluation of underlying diseases and medications in different wards of a large Urban Hospital Center in Iran. *BMC Anesthesiol*. (2022) 22:147. doi: 10.1186/s12871-022-01690-w

17. Cartei A, Mossello E, Ceccofiglio A, Rubbieri G, Polidori G, Ranalli C, et al. Independent, differential effects of delirium on disability and mortality risk after hip fracture. *J Am Med Dir Assoc*. (2022) 23:654–659.e1. doi: 10.1016/j.jamda.2021.10.021

18. Silva LOJE, Berning MJ, Stanich JA, Gerberi DJ, Murad MH, Han JH, et al. Risk factors for delirium in older adults in the emergency department: a systematic review and Meta-analysis. *Ann Emerg Med*. (2021) 78:549–65. doi: 10.1016/j.annemergmed.2021.03.005

19. Shenkin SD, Fox C, Godfrey M, Siddiqi N, Goodacre S, Young J, et al. Delirium detection in older acute medical inpatients: a multicentre prospective comparative diagnostic test accuracy study of the 4AT and the confusion assessment method. *BMC Med*. (2019) 17:138. doi: 10.1186/s12916-019-1367-9

20. Jeong E, Park J, Lee J. Diagnostic test accuracy of the 4AT for delirium detection: a systematic review and Meta-analysis. *Int J Environ Res Public Health*. (2020) 17:7515. doi: 10.3390/ijerph17207515

21. Bellelli G, Morandi A, Davis DHJ, Mazzola P, Turco R, Gentile S, et al. Validation of the 4AT, a new instrument for rapid delirium screening: a study in 234 hospitalised older people. *Age Ageing*. (2014) 43:496–502. doi: 10.1093/ageing/afu021

22. Carpenter CR, Hammouda N, Linton EA, Doering M, Ohuabunwa UK, Ko KJ, et al. Delirium prevention, detection, and treatment in emergency medicine settings: a geriatric emergency care applied research (GEAR) network scoping review and consensus statement. *Acad Emerg Med*. (2021) 28:19–35. doi: 10.1111/acem.14166

23. Ahmed S, Leurent B, Sampson EL. Risk factors for incident delirium among older people in acute hospital medical units: a systematic review and meta-analysis. *Age Ageing*. (2014) 43:326–33. doi: 10.1093/ageing/afu022

24. Vardy E, Collins N, Grover U, Thompson R, Bagnall A, Clarke G, et al. Use of a digital delirium pathway and quality improvement to improve delirium detection in the emergency department and outcomes in an acute hospital. *Age Ageing*. (2020) 49:672–8. doi: 10.1093/ageing/afaa069

25. APS J, Batista REA, Campanharo CRV, Lopes MCBT, Okuno MFP. Evaluation of the Manchester triage system quality indicator: service time. *Rev Gaucha Enferm*. (2021) 42:e20200371. doi: 10.1590/1983-1447.2021.20200371

26. O'Shaughnessy Í, Romero-Ortuno R, Edge L, Dillon A, Flynn S, Briggs R, et al. Home FIRsT: interdisciplinary geriatric assessment and disposition outcomes in the emergency department. *Eur J Intern Med*. (2021) 85:50–5. doi: 10.1016/j.ejim.2020.11.015

27. Möckel M, Reiter S, Lindner T, Slagman A. Triagierung– Ersteinschätzung von Patienten in der zentralen Notaufnahme. *Med Klin Intensivmed Notfmed*. (2020) 115:668–81. doi: 10.1007/s00063-019-0589-0

28. Lucke JA, Mooijaart SP, Conroy S, Blomaard LC, De Groot B, Nickel CH. Mortality risk for different presenting complaints amongst older patients assessed with the Manchester triage system. *Eur Geriatr Med*. (2021) 13:323–8. doi: 10.1007/s41999-021-00568-3

29. Wolf LA, Delao AM, Malsch AJ, Moon MD, Perry A, Zavotsky KE. Emergency nurses' perception of geriatric readiness in the ED setting: a mixed-methods study. *J Emerg Nurs*. (2019) 45:374–85. doi: 10.1016/j.jen.2019.02.004

30. Evensen S, Saltvedt I, Ranhoff AH, Myrstad M, Myrstad C, Mellingsæter M, et al. Delirium and cognitive impairment among older patients in Norwegian emergency departments. *Tidsskr Nor Laegeforen*. (2019) 139:578. doi: 10.4045/tidsskr.18.0578

31. Calf AH, Pouw MA, van Munster BC, Burgerhof JGM, de Rooij SE, Smidt N. Screening instruments for cognitive impairment in older patients in the emergency department: a systematic review and meta-analysis. *Age Ageing*. (2021) 50:105–12. doi: 10.1093/ageing/afaa183

32. Tieges Z, Maclullich AMJ, Anand A, Brookes C, Cassarino M, O'connor M, et al. Diagnostic accuracy of the 4AT for delirium detection in older adults: systematic review and meta-analysis. *Age Ageing*. (2021) 50:733–43. doi: 10.1093/ageing/afaa224

33. Lee S, Gottlieb M, Mulhausen P, Wilbur J, Reisinger HS, Han JH, et al. Recognition, prevention, and treatment of delirium in emergency department: an evidence-based narrative review. *Am J Emerg Med*. (2020) 38:349–57. doi: 10.1016/j.ajem.2019.158454

34. Artola CB, Solórzano NG, Chaves AA. Delirium en el adulto mayor. *Rev Méd Sinerg*. (2020) 5:391–1. doi: 10.31434/rms.v5i3.391

35. Kaeppeli T, Rueegg M, Dreher-Hummel T, Brabrand M, Kabell-Nissen S, Carpenter CR, et al. Validation of the clinical frailty scale for prediction of thirty-day mortality in the emergency department. *Ann Emerg Med*. (2020) 76:291–300. doi: 10.1016/j.annemergmed.2020.03.028

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Interpretable machine learning model for early prediction of delirium in elderly patients following intensive care unit admission: a derivation and validation study

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Background and objective: Delirium is the most common neuropsychological complication among older adults admitted to the intensive care unit (ICU) and is often associated with a poor prognosis. This study aimed to construct and validate an interpretable machine learning (ML) for early delirium prediction in older ICU patients.

Methods: This was a retrospective observational cohort study and patient data were extracted from the Medical Information Mart for Intensive Care-IV database. Feature variables associated with delirium, including predisposing factors, disease-related factors, and iatrogenic and environmental factors, were selected using least absolute shrinkage and selection operator regression, and prediction models were built using logistic regression, decision trees, support vector machines, extreme gradient boosting (XGBoost), k-nearest neighbors and naive Bayes methods. Multiple metrics were used for evaluation of performance of the models, including the area under the receiver operating characteristic curve (AUC), accuracy, sensitivity, specificity, recall, F1 score, calibration plot, and decision curve analysis. SHapley Additive exPlanations (SHAP) were used to improve the interpretability of the final model.

Results: Nine thousand seven hundred forty-eight adults aged 65 years or older were included for analysis. Twenty-six features were selected to construct ML prediction models. Among the models compared, the XGBoost model demonstrated the best performance including the highest AUC (0.836), accuracy (0.765), sensitivity (0.713), recall (0.713), and F1 score (0.725) in the training set. It also exhibited excellent discrimination with AUC of 0.810, good calibration, and had the highest net benefit in the validation cohort. The SHAP summary analysis showed that Glasgow Coma Scale, mechanical ventilation, and sedation were the top three risk features for outcome prediction. The SHAP dependency plot and SHAP force analysis interpreted the model at both the factor level and individual level, respectively.

Conclusion: ML is a reliable tool for predicting the risk of critical delirium in elderly patients. By combining XGBoost and SHAP, it can provide clear explanations for personalized risk prediction and more intuitive understanding of the effect of key features in the model. The establishment of such a model would facilitate the early risk assessment and prompt intervention for delirium.

KEYWORDS
elderly, delirium, ICU, prediction model, explainable machine learning

Introduction

Delirium, also known as acute encephalopathy, is a neuropsychiatric syndrome characterized by acute changes or fluctuations of cognitive function, inattention, disorganized thinking, and altered level of consciousness (1, 2). Delirium is highly prevalent among hospitalized older adults and represents the most common neuropsychological complication in older patients within the intensive care unit (ICU) (3). Reported incidence rates of delirium among hospitalized older adults ranges from 14 to 56%, depending on patient population and screening instrument (4–6). In the ICU, the prevalence of delirium has been shown to reach as high as 60–80% (3, 7). Delirium in older patients often arises due to a complex interplay of factors exacerbating challenges posed by the ICU environment, including prolonged mechanical ventilation (MV) and hospital stay, increased costs, long-term cognitive impairment, and increased risk of death (8, 9).

It is now known that antipsychotics and other psychoactive medications do not reliably improve brain function in critically ill patients with delirium (10). According to the 2018 Pain, Agitation/Sedation, Delirium, Immobility, and Sleep Disorders in Adult Patients in the ICU Guideline, clinicians need to pay increased attention to the screening of high-risk delirium patients and actively implementing approaches to prevent delirium (11). Therefore, a reliable delirium predictive model will help clinicians identify delirium high-risk patients and guide timely interventions. In fact, several predictive models have been developed for delirium in the ICU, including the PRE-DELIRIC model, the E-PRE-DELIRIC model, and the DYNAMIC-ICU model (12–15). However, all of these models were based on results from a wide range of age groups and did not take into consideration the characteristics of older patients. There are other alternative models available for predicting delirium in older adults, but these models have been mainly validated in postoperative individuals, and their applicability to ICU patients is still uncertain (16–19). Therefore, there is still a lack of delirium risk prediction models applicable to older patients admitted to the ICU.

Compared to traditional regression analysis, machine learning (ML) methods offer numerous potential advantages for studies of older adults (20). With the abundance of data available from geriatric cohort studies and electronic health records, ML methods can enhance the accuracy and efficiency of prediction models in aging applications while leveraging the increasing amounts of health system data (21). However, due to the "black box" of ML algorithms, this makes it difficult to understand the predicted outcomes and limits the applications of these models (18). Notably, the SHapley Additive exPlanation (SHAP) methods have gained increasing prominence in addressing this issue (19). SHAP has significant advantages in elucidating how the ML model calculates the features required for prediction and visualizing the prediction models. It has been successfully applied to improve clinical understanding of a variety of diseases, including the risk of hypoxemia during surgery, the prognosis of acute kidney injury, and the risk factors for sepsis and septic death (22–24). However, there is currently no interpretable ML method to predict the risk of delirium in critically ill older patients.

The objective of this study was to develop and validate a predictive model for delirium in ICU patients aged 65 years and older using six ML algorithms. In addition, the SHAP method was used to provide a comprehensive explanation and enhancing clinical understanding for the best performing model. The findings from this study would facilitate early identification of high-risk older individuals prone to delirium in ICU settings, thereby enabling clinicians to implement timely interventions.

Materials and methods

Data source

The study was conducted using the extensive electronic health record database of the Medical Information Mart for Intensive Care (MIMIC)-IV version 2.2 (v2.2). Specifically, the MIMIC database contains comprehensive and high-quality data on both deidentified and characterized adult patients (≥18 years old) who were admitted to the ICU at Beth Israel Deaconess Medical Center between 2008 and 2019 (25). MIMIC-IV v2.2 is the latest version of the MIMIC database, incorporating contemporary data (26). The institutional review board at MIT (Cambridge, MA) and Beth Israel Deaconess Medical Center (Boston, MA) approved the use of this database, granting a waiver of informed consent for this study while ensuring compliance with ethical standards outlined in the Declaration of Helsinki. One of our authors has been granted access to the database (CM, Certification Number: 34907227). Our study adhered to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement (27).

Study population and outcome

Older patients were included if they met the following criteria: (1) admitted to the ICU; (2) underwent delirium assessment; (3) aged ≥65 years older. The assessment of delirium in the MIMIC-IV v2.2 database was conducted using the Confusion Assessment Method for the ICU (CAM-ICU) score. The CAM-ICU score is the most effective tool for diagnosing and assessing delirium in adult ICU patients according to the 2013 Society of Critical Care Medicine guidelines for pain, agitation, and delirium, which consists of four features: (1) an acute onset of mental status changes or a fluctuating course; (2) inattention; (3) disorganized thinking; and (4) an altered level of consciousness (28). Patients were diagnosed with delirium (i.e., CAM-ICU positive) if they presented with features 1 and 2, in addition to either feature 3 or 4. We excluded patients who had been hospitalized for less than 48 h and those already diagnosed with dementia, as the latter can be easily misdiagnosed as cognitive

impairment. In cases where patients had multiple admissions to the ICU, only their first admission was analyzed.

This is a retrospective observational study in which all enrolled patients have undergone delirium assessment. They were further divided into two groups: delirious patients (case group) and non-delirious patients (control group), and a comparison of baseline characteristics between the two groups was conducted (see Table 1). The primary outcome of this study was the occurrence of delirium during ICU stay. All enrolled patients were followed from inclusion until ICU discharge, hospital discharge, or in-hospital death.

Data extraction and variables processing

In order to maximize the collection of potential candidate delirium predictors, we conducted a comprehensive literature review to summarize the risk factors for delirium. According to the widely accepted classification of risk factors for delirium, these factors can be categorized into three major groups: predisposing factors, disease-related factors, and iatrogenic and environmental factors (6, 29). Old age, gender, body mass index, marital status, education level, and a high burden of coexisting conditions are common predisposing factors (1, 6, 30, 31). The presence of certain chronic comorbidities, such as chronic obstructive pulmonary disease (COPD), hypertension, diabetes, heart failure, atrial fibrillation (AF), stroke, chronic kidney disease (CKD), and tumor has also been associated with the development of delirium (6, 29, 32). The disease-related factors encompass the severity of the disease upon admission and laboratory indicators after admission, including blood routine count, creatinine, electrolyte, albumin, blood glucose, and coagulation indicators (30, 32, 33). The vital signs, including blood pressure, heart rate, respiratory rate, and temperature, are commonly reported as well (34, 35). The iatrogenic and environmental factors involve interventions received in ICUs, including drugs and organ support techniques, such as the utilization of sedatives and vasoactive drugs, and implementation of MV and renal replace therapy (RRT) (6, 29, 36).

Based on the aforementioned delirium-related variables, we utilized structured query language (SQL) with PostgreSQL (version 9.6) to extract the following data from the MIMV-IV v2.2 database: demographic characteristics (including age, gender, race, and marital status), admission condition (including admission type and ICU type), chronic comorbidities, disease severity scores, vital signs and laboratory indicators within 24 h after ICU admission. The vital signs were determined as the mean values during the first 24 h since ICU admission of each included patients. In cases where a laboratory variable was recorded multiple times within this time frame, the value corresponding to the greatest severity of illness was selected. Additionally, we documented the occurrence of acute kidney injury and ICU interventions within 48 h of ICU admission, such as MV, RRT, vasopressors, and sedation.

Our study was retrospective and relied on existing clinical data, no formal sample size calculation was performed prior to the study. Instead, we collected as many samples from the database as possible. Ultimately, a total of 9,748 patients were enrolled in the study. And 48 variables were collected for preliminary analysis (Table 1). Given that this study focuses on a binary outcome, the sample size of the final cohort is adequate to ensure the robustness of the results while adhering to the principle of having at least 10 events per variable (EPV) (37, 38). Variables with missing data exceeding 20% were excluded (39). The remaining missing values underwent multiple imputation using "MICE" package in R (40). Details of missing data was shown in Supplementary Figure S1.

Statistical analyses

Continuous variables in this study were reported as medians with interquartile range (IQR) unless otherwise specified, and the differences between groups were identified with univariate analysis. Categorical variables were presented as frequency and proportion in each patient group, and compared using the chi-square test or Fisher's exact test if appropriate. All statistical analyses were performed using the R software (version 4.3.2). *p*-values less than 0.05 (two-sided test) were considered statistically significant.

A pre-seeded random number generator (123) in R software was utilized to randomly divide the cohort into training ($n = 6,823$) and validation ($n = 2,925$) sets based on a ratio of 7:3. All patients in the training set were included for variables selection and model development. We employed an L1-penalty least absolute shrinkage and selection operator (LASSO) regression approach to reduce potential collinearities and prevent overfitting, augmented with 10-fold cross-validation (41). LASSO regression is a method used to reduce the dimensionality of data by selecting features based on a penalty function. It effectively reduces the absolute size of the coefficients in a regression model, determined by the value of lambda. Following the feature selection, we identified 26 features with significant predictive ability according to lambda. 1se criterion. The prediction model was then constructed using the following ML algorithm, including logistic regression (LR), decision trees (DT), support vector machines (SVM), extreme gradient boosting (XGBoost), k-nearest neighbors (KNN), and naive Bayes (NB). ML have the capacity to accommodate numerous predictors, fewer model assumptions, and require less user specification of model terms. It has the ability to form flexible, empirically driven interactions based on the data without needing these interactions to be specified in advance (20). During the modeling process, we repeated 5 rounds of 10-fold cross-validation and grid search parameter optimization to ensure stability.

The area under receiver operating characteristic (ROC) curve (AUC), accuracy, specificity, sensitivity, positive predictive value (PPV), negative predictive value (NPV), recall, and F1 score were used to assess the model's performance. The optimal model was determined based on the highest AUC and accuracy in the validation set (42, 43). We then utilized a calibration curve to evaluate the consistency between predicted and actual occurrence of delirium for the top three optimal models in the training set. Additionally, we assessed the net clinical benefit through the decision curve analysis (DCA).

SHAP method is applied to interpret the optimal model. The SHAP values are derived from game theory, providing an estimation of the impact that each feature has on the predicted outcome and effectively explaining the contribution of each feature to a single observation (19, 44). We employed a SHAP significance analysis and SHAP summary plot to evaluate feature importance, followed by utilizing SHAP dependency plot to investigate the impact of features on outcome prediction. Finally, a SHAP force analysis was used to elucidate the contribution of features in individual patients.

TABLE 1 Baseline characteristics of patients with and without delirium.

Variables	Total (*N* = 9,748)	Non-delirium (*N* = 5,505)	Delirium (*N* = 4,243)	*p*-value
Age (years)	76 (70, 83)	76 (70, 82)	76 (71, 83)	0.004
Male (%)	5,277 (54.1)	2,970 (54.0)	2,307 (54.4)	0.7
Ethnicity (%)				<0.001
Asian	1,688 (17.3)	841 (15.3)	847 (20.0)	
Black	765 (7.8)	390 (7.1)	375 (8.8)	
Hispanic	210 (2.2)	123 (2.2)	87 (2.1)	
White	6,665 (68.4)	3,900 (70.8)	2,765 (65.2)	
Others	420 (4.3)	251 (4.6)	169 (4.0)	
Marital Status (%)				<0.001
Single	2,476 (25.4)	1,278 (23.2)	1,198 (28.2)	
Married	4,771 (48.9)	2,801 (50.9)	1,970 (46.4)	
Divorced	658 (6.8)	378 (6.9)	280 (6.6)	
Others	1,843 (18.9)	1,048 (19.0)	795 (18.7)	
Admission type (%)				<0.001
Selective	1,538 (15.8)	1,025 (18.6)	513 (12.1)	
Urgent	7,850 (80.5)	4,244 (77.1)	3,606 (85.0)	
Emergent	360 (3.7)	236 (4.3)	124 (2.9)	
ICU type (%)				<0.001
CVICU	2,207 (22.6)	1,498 (27.2)	709 (16.7)	
CCU	1,405 (14.4)	941 (17.1)	464 (10.9)	
MICU	1,457 (14.9)	660 (12.0)	797 (18.8)	
M/SICU	1,317 (13.5)	735 (13.4)	582 (13.7)	
NICU	1,050 (10.8)	550 (10.0)	500 (11.8)	
SICU	1,286 (13.2)	629 (11.4)	657 (15.5)	
TSICU	1,026 (10.5)	492 (8.9)	534 (12.6)	
Comorbidity				
COPD (%)	1,133 (11.6)	541 (9.8)	592 (14.0)	<0.001
Hypertension (%)	4,638 (47.6)	2,698 (49.0)	1,940 (45.7)	0.001
Diabetes (%)	3,238 (33.2)	1,736 (31.5)	1,502 (35.4)	<0.001
Heart failure (%)	3,706 (38.0)	2,057 (37.4)	1,649 (38.9)	0.13
Atrial fibrillation (%)	4,397 (45.1)	2,396 (43.5)	2,001 (47.2)	<0.001
AMI (%)	1,448 (14.9)	776 (14.1)	672 (15.8)	0.017
CKD (%)	2,419 (24.8)	1,268 (23.0)	1,151 (27.1)	<0.001
Stroke (%)	2,112 (21.7)	990 (18.0)	1,122 (26.4)	<0.001
Tumor (%)	1,483 (15.2)	854 (15.5)	629 (14.8)	0.3
Scoring system				
GCS	15.0 (14.0, 15.0)	15.0 (14.0, 15.0)	14.0 (13.0, 15.0)	<0.001
APSIII	43 (33, 56)	39 (31, 51)	49 (37, 63)	<0.001
SAPS II	39 (32, 48)	37 (31, 44)	43 (36, 52)	<0.001
SOFA	5.0 (3.0, 7.0)	4.0 (2.0, 6.0)	6.0 (4.0, 9.0)	<0.001
Vital signs				
Heart rate (min^{-1})	81 (72, 92)	80 (72, 91)	83 (74, 95)	<0.001
Systolic BP (mmHg)	116 (106, 128)	115 (106, 128)	116 (106, 128)	0.2
Diastolic BP (mmHg)	59 (53, 67)	59 (53, 67)	59 (54, 67)	0.3

(Continued)

TABLE 1 (Continued)

Variables	Total (*N* = 9,748)	Non-delirium (*N* = 5,505)	Delirium (*N* = 4,243)	*p*-value
Mean BP (mmHg)	75 (70, 83)	75 (70, 83)	76 (70, 83)	0.11
Respiratory (min^{-1})	18.8 (16.8, 21.3)	18.6 (16.6, 21.0)	19.1 (17.0, 21.7)	<0.001
Temperature (°C)	36.8 (36.6, 37.1)	36.8 (36.6, 37.0)	36.9 (36.6, 37.2)	<0.001
Lab. indicators				
WBC (10^9/L)	11.3 (8.4, 15.0)	10.9 (8.1, 14.5)	11.8 (8.9, 15.5)	<0.001
Hemoglobin (10^{12}/L)	10.45 (9.15, 12.00)	10.45 (9.20, 12.00)	10.45 (9.05, 12.00)	0.2
Hematocrit (%)	32.0 (28.1, 36.7)	32.0 (28.2, 36.5)	32.2 (28.0, 36.8)	0.4
Platelet (10^9/L)	180 (135, 239)	180 (136, 238)	180 (135, 241)	0.6
Bicarbonate (mmol/L)	23.0 (20.5, 25.0)	23.0 (21.0, 25.0)	22.5 (20.0, 24.5)	<0.001
Sodium (mmol/L)	138.5 (136.0, 141.0)	138.5 (136.0, 140.5)	139.0 (136.0, 141.5)	<0.001
Potassium (mmol/L)	4.20 (3.90, 4.60)	4.20 (3.90, 4.60)	4.20 (3.90, 4.65)	0.12
Chloride (mmol/L)	104.0 (100.0, 107.5)	104.0 (100.5, 107.0)	104.0 (100.0, 107.5)	0.5
Calcium (mmol/L)	8.40 (7.95, 8.85)	8.40 (7.98, 8.85)	8.35 (7.90, 8.80)	<0.001
Glucose (mg/dL)	132 (111, 163)	128 (109, 155)	138 (115, 173)	<0.001
BUN (mg/dL)	22 (16, 34)	21 (15, 31)	23 (17, 38)	<0.001
Creatinine (mg/dL)	1.05 (0.80, 1.55)	1.00 (0.75, 1.40)	1.10 (0.80, 1.75)	<0.001
Anion gap (mmol/L)	14.5 (12.5, 17.0)	14.0 (12.0, 16.0)	15.0 (13.0, 17.5)	<0.001
INR	1.25 (1.10, 1.50)	1.25 (1.10, 1.45)	1.30 (1.10, 1.55)	0.003
Prothrombin time (s)	13.8 (12.2, 16.3)	13.8 (12.2, 16.0)	13.9 (12.2, 16.8)	0.023
PTT (s)	32 (28, 42)	32 (28, 42)	32 (28, 41)	0.021
ICU interventions				
MV (%)	4,517 (46.3)	1,862 (33.8)	2,655 (62.6)	<0.001
RRT (%)	420 (4.3)	164 (3.0)	256 (6.0)	<0.001
Vasopressor use (%)	4,522 (46.4)	2,282 (41.5)	2,240 (52.8)	<0.001
Sedation (%)	5,239 (53.7)	2,345 (42.6)	2,894 (68.2)	<0.001
AKI (%)	7,007 (71.9)	3,699 (67.2)	3,308 (78.0)	<0.001
ICU-stay (days)	3.7 (2.6, 6.1)	3.1 (2.3, 4.2)	5.3 (3.3, 9.5)	<0.001
Hospital-stay (days)	9 (6, 15)	8 (5, 12)	12 (8, 20)	<0.001
ICU-mortality (%)	865 (8.9)	315 (5.7)	550 (13.0)	<0.001
Hospital-mortality (%)	1,486 (15.2)	551 (10.0)	935 (22.0)	<0.001

Data are presented as a number with the percentage in parentheses, or as the median with the interquartile range in parentheses. The "tumor" refers to a malignant cancer. Sedation includes midazolam, propofol, dexmedetomidine, and diazepam. ICU, intensive care unit; CCU, coronary care unit; CVICU, cardiovascular ICU; MICU, medical ICU; SICU, surgical ICU; NICU, neuro ICU; TSICU, trauma-neuro surgical ICU; COPD, chronic obstructive pulmonary disease; AMI, acute myocardial infarction; CKD, chronic kidney disease; GCS, Glasgow Coma Score; APSIII, the Acute Physiology Score III; SAPS II, the Simplified Acute Physiology Score II; SOFA, the Sequential Organ Failure Assessment score; BP, blood pressure; SpO_2, oxyhemoglobin saturation; WBC, white blood cell count; BUN, blood urea nitrogen; INR, international normalized ratio; PTT, partial thromboplastin time; MV, mechanical ventilation; RRT, renal replacement therapy; AKI, acute kidney injury.

Results

Baseline characteristics

A total of 9,748 older patients from the MIMIC-IV v2.2 database were eventually included in this study and the detailed selection process could be found in Figure 1. Among the enrolled patients, there were 4,243 cases of delirium (43.5%). Table 1 summarizes the characteristics of patients with and without delirium, including the demographic, comorbidity, disease-related conditions, and the ICU interventions. Overall, patients with delirium had had higher white blood cell, blood urea nitrogen, creatinine, anion gap, international normalized ratio and glucose levels, and were more likely to have COPD, cerebrovascular disease, diabetes, CKD, and stroke, and received more medical treatment. They also exhibited more abnormal vital signs and electrolyte levels, as well as a higher degree of disease severity. The length of the ICU and hospital day in the delirium group was significantly longer than that in the non-delirium group [ICU-stay: 5.3 (3.3, 9.5) vs. 3.1 (2.3, 4.2), $p < 0.001$; hospital-stay: 12 (8, 20) vs. 8 (5, 12), $p < 0.001$]. Similarly, there were significant difference in mortality between delirium and non-delirium groups (ICU mortality: 13.0% vs. 5.7%, $p < 0.001$; hospital mortality: 22.0% vs. 10.0%,

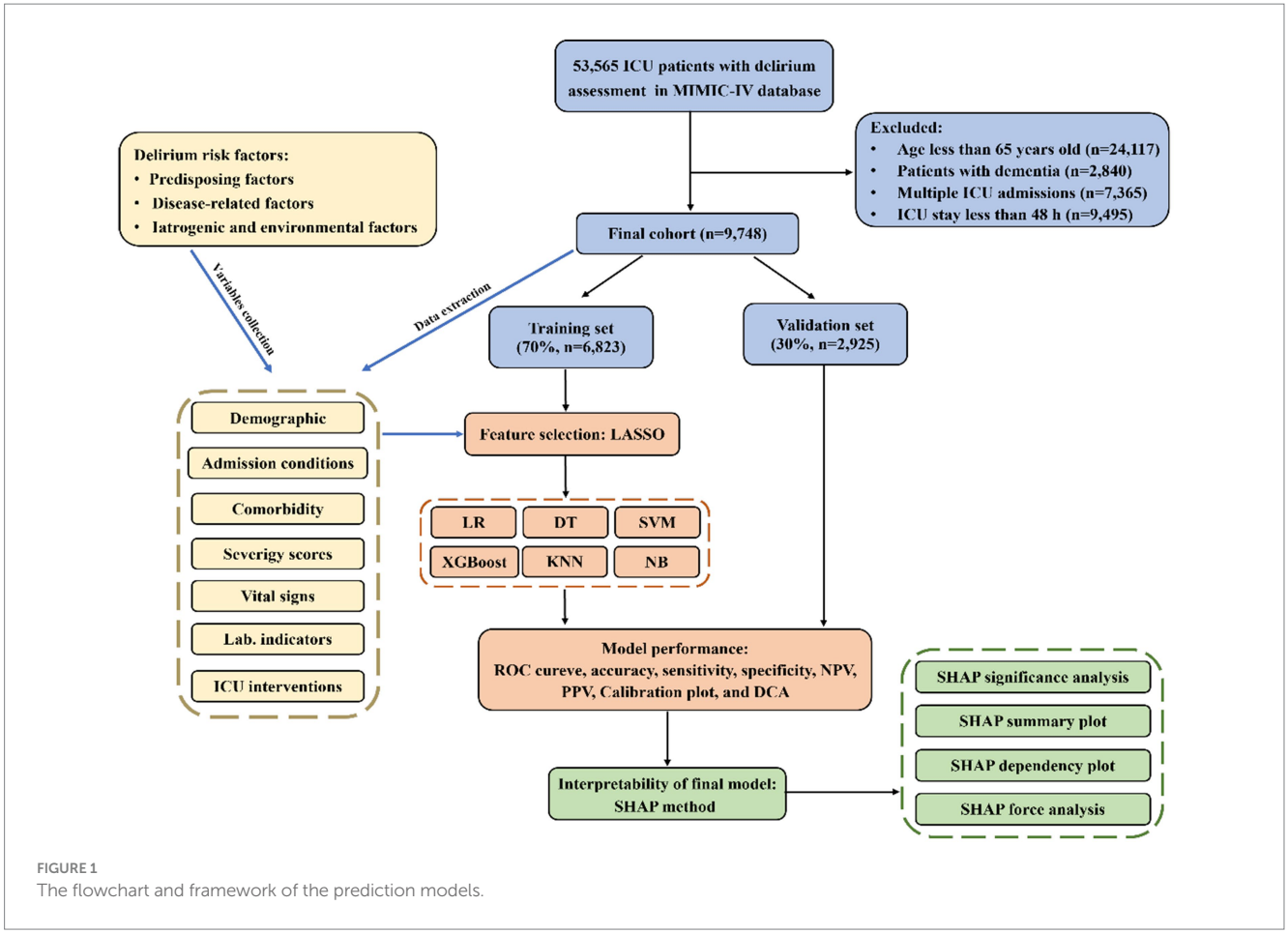

FIGURE 1
The flowchart and framework of the prediction models.

$p < 0.001$), which suggests that delirium may be associated with a poor prognosis.

The total population was divided into a 70% training cohort and a 30% validation cohort, with comparable baseline characteristics between the two sets ($p > 0.05$), as detailed in Supplementary Table S1. The training set was subsequently utilized for model development.

Feature selection and model development

To identify the most relevant variables for critical delirium in Table 1, we employed L1-penalized LASSO regression for dimensionality reduction and feature selection. Figure 2A illustrates the relationship between cross-validation errors and penalty terms. We utilized a 10-fold cross-validation approach to determine the optimal penalty parameter lambda, selecting 26 clinical variables with significant predictive ability based on the lambda. 1se criteria to construct our model. Figure 2B displays the distribution of coefficients for these selected features in the LASSO regression, revealing the optimal point for retaining nonzero variables. The Supplementary Table S2 presents the 26 selected variables, along with their corresponding non-zero coefficient values.

Subsequently, based on the selected features, we employed six ML algorithms, including LR, DT, SVM, XGBoost, KNN, and NB, to predict the primary outcome from the training set. During the modeling process, we performed 5 rounds of 10-fold cross-validation and grid search parameter optimization to ensure the generalizability of the models while avoiding overfitting.

Model performance and comparisons

The performance comparison of various ML models was presented in Table 2 and Figure 3, respectively. Table 2 provides the detailed AUC, accuracy, sensitivity, specificity, PPV, NPV, recall, and F1 scores for six models. The AUC values associated with the different models ranged from 0.777 to 0.836 (LR: 0.777, DT: 0.791, SVM: 0.785, XGBoost: 0.836, KNN: 0.799, and NB: 0.777) in the training set (Figure 3A). The XGBoost model had the highest performance with an AUC of 0.836, accuracy of 0.765, sensitivity of 0.713, recall of 0.713, and F1 score of 0.725 (Table 2). Similarly, in the validation set, the XGBoost model achieved the highest performance with an AUC of 0.810 and accuracy of 0.744, which surpassed the AUCs of the other models, highlighting the superior performance of the XGBoost model (Table 2 and Figure 3B).

To examine the calibration of the models, calibration curves for the three models with the highest AUC values (XGBoost, KNN, DT) were generated and compared (Figure 3C). Among them, XGBoost showed the best fit between observed and predicted probabilities, indicating its superior calibration. Decision curve analysis (DCA) was performed on these three models and the results are shown in Figure 3D. The analysis showed that using the XGBoost prediction

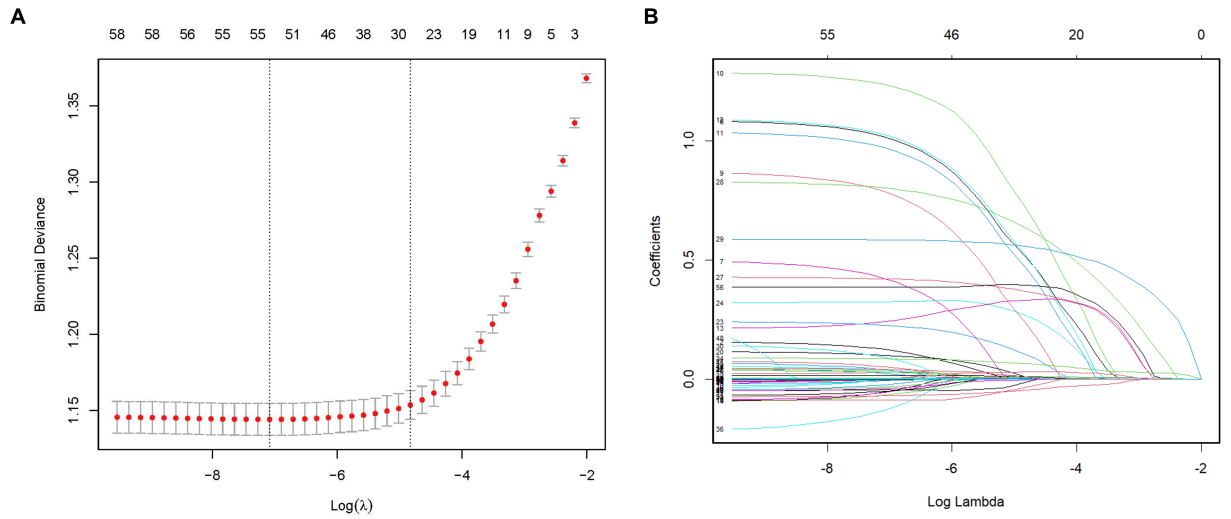

FIGURE 2
Feature selection by the LASSO regression model. **(A)** The LASSO model underwent tenfold cross-validation to determine the optimal penalization coefficient parameter (lambda). **(B)** The plots depict the LASSO regression coefficients across various penalty parameter values. The lambda. 1se was chosen in our study due to its stricter penalty and ability to reduce overfitting. LASSO, least absolute shrinkage and selection operator.

TABLE 2 The prediction performance of each model.

Model	AUC	Accuracy	Sensitivity	Specificity	PPV	NPV	Recall	F1 score
Training set								
LR	0.777	0.713	0.599	0.801	0.698	0.722	0.599	0.645
XGBoost	0.836	0.765	0.713	0.804	0.737	0.785	0.713	0.725
DT	0.791	0.724	0.683	0.755	0.682	0.756	0.683	0.683
SVM	0.785	0.721	0.636	0.787	0.696	0.738	0.636	0.665
KNN	0.799	0.719	0.519	0.873	0.758	0.703	0.519	0.616
NB	0.777	0.678	0.399	0.892	0.739	0.659	0.399	0.518
Validation set								
LR	0.780	0.715	0.602	0.804	0.704	0.722	0.602	0.649
XGBoost	0.810	0.744	0.692	0.785	0.715	0.766	0.692	0.703
DT	0.792	0.722	0.671	0.761	0.686	0.748	0.671	0.679
SVM	0.785	0.720	0.638	0.785	0.697	0.736	0.638	0.666
KNN	0.772	0.700	0.498	0.858	0.731	0.687	0.498	0.592
NB	0.761	0.662	0.385	0.878	0.710	0.647	0.385	0.499

LR, logistic regression; XGBoost, extreme gradient boosting; DT, decision tree; SVM, support vector machine; KNN, k-nearest neighbors; NB, naive bayes.

model provided the highest net benefit for predicting delirium, outperforming both KNN and DT. Taken together, the XGBoost model was selected as the optimal model and subsequently employed for further interpretation.

Model interpretations

The predictor's contribution to the prediction outcomes was quantified using SHAP, which employs a game-theoretic approach to assess the significance of each feature. The feature importance ranking was visualized using the SHAP significance analysis for the XGBoost model, as depicted in Figure 4A. Our analysis identified the top 10 risk factors associated with critical delirium, including Glasgow Coma Scale (GCS) score, MV, sedation, ICU type, the Acute Physiology Score III (APSIII), temperature, age, diastolic blood pressure, oxyhemoglobin saturation and the Sequential Organ Failure Assessment score (SOFA). This ranking was further complemented by SHAP summary plot (Figure 4B) that visually demonstrates the influence of each feature on model output. A positive Shapley value for each feature indicates an increased risk of delirium while a negative value suggests decreased risk. For instance, for MV, yellow dots located rightward from zero line signifies higher MV values (i.e., receiving MV treatment) contributing towards increased risks of delirium.

The impact of features at factor level on the risk of the predictive model was analyzed using SHAP dependency plot, as depicted in

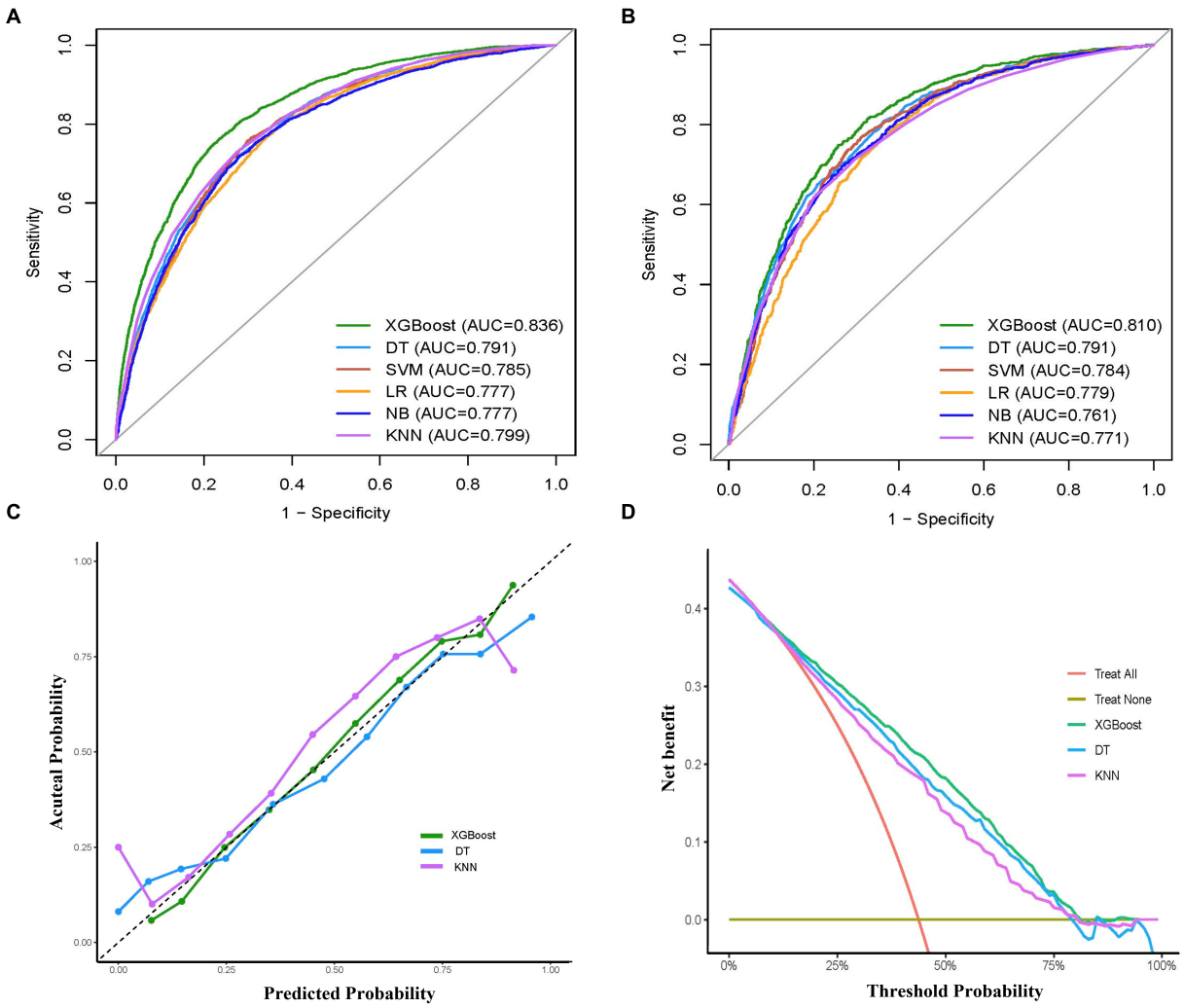

FIGURE 3
Comprehensive evaluation of machine learning models. **(A)** ROC curves and AUC values of the training set. **(B)** ROC curves and AUC values of the validation set. **(C)** Calibration curves of the XGBoost, DT, KNN models in the validation set. **(D)** Decision curves analysis of the XGBoost, RF, SVM models in the validation set. ROC, receiver operating characteristic; AUC, the area under the receiver operating characteristic curve; LR, logistic regression; XGBoost, extreme gradient boosting; DT, decision tree; SVM, support vector machine; KNN, k-nearest neighbors; NB, naive bayes.

Figure 5. The three most important features in the XGBoost model, namely GCS, MV, and sedation, were depicted in Figures 5A–C respectively. The results showed a complex nonlinear relationship between GCS and outcomes, while MV and sedation were consistently associated with increased risk. APSIII score is a widely used tool to assess the severity of patients in the ICU. Using the APSIII score as an example, Figures 5D–F furthermore illustrated interactions among different features. It was evident that despite identical APSIII scores, there may be discrepancies in the corresponding SHAP values for different levels of GCS, MV and sedation.

Additionally, we further demonstrate the model's interpretability by presenting SHAP force analysis for two representative cases: one predicting a high risk of delirium and another indicating a low risk of delirium (Supplementary Figure S2). The plot provides an overview of how the key features affect prediction outcome at individual level. Factors that contribute to higher predicted scores compared with the baseline (mean predicted value) are highlighted in purple, while factors that lead to lower predicted scores are indicated in orange. The length of the arrows helps visualize the degree of impact of the prediction, whereby the longer the arrow, the more significant the effect. For instance, in the first case (Supplementary Figure S2A), most features are shown in purple, suggesting their contribution to the risk of developing delirium, particularly blood urea nitrogen and APSIII.

Discussion

In this retrospective cohort study, we used ML methods to establish a clinical prediction model for assessing the risk of delirium in ICU patients aged 65 years and older. The ML prediction model based on XGBoost was ultimately chosen due to its impressive performance in predicting delirium. In addition, we further used the SHAP value method to gain a deeper understanding of the prediction model. To the best of our knowledge, this study is the first to develop a prediction model for delirium in older patients in the ICU through explainable ML methods. These findings could help healthcare

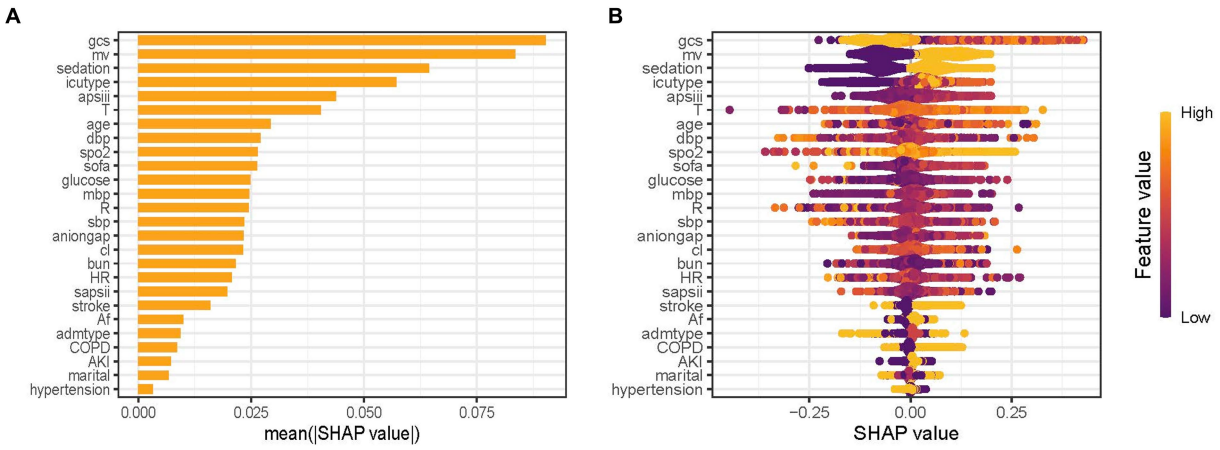

FIGURE 4
Feature importance analysis by SHAP method for XGBoost model. **(A)** SHAP significance analysis of feature importance ranking based on the mean value. **(B)** SHAP summary plot of the XGBoost model. GCS, Glasgow Coma Scale; MV, mechanical ventilation; APSIII, the Acute Physiology Score III; T, temperature; DBP, diastolic blood pressure; SpO_2, oxyhemoglobin saturation; SOFA, the Sequential Organ Failure Assessment Score; MBP, mean blood pressure; R, respiratory rate; SBP, systolic blood pressure; Cl, chloride; BUN, blood urea nitrogen; HR, heart rate; SAPSII, the Simplified Acute Physiology Score II; AF, Atrial fibrillation; Admtype, type of admission; COPD, chronic obstructive pulmonary disease; AKI, acute kidney injury.

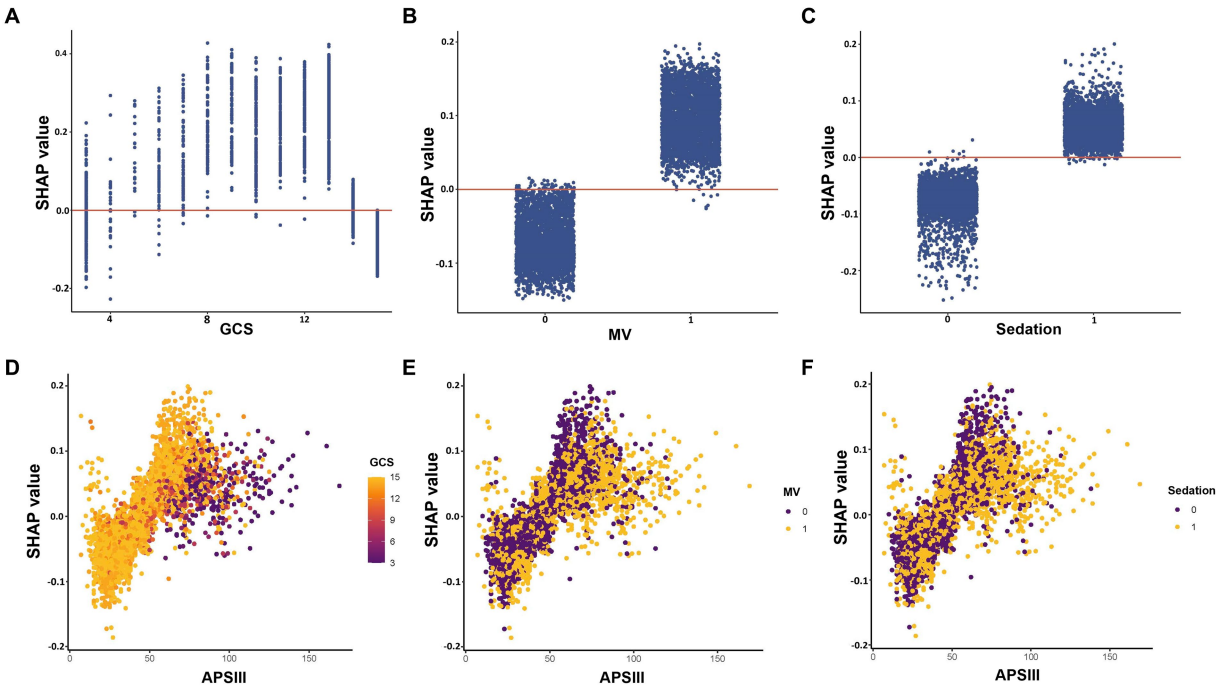

FIGURE 5
SHAP dependency plot of features in the XGBoost model. The *Y*-axis represents SHAP values, while the *X*-axis represents actual clinical parameters. For binary variables such as MV and sedation, "0" indicates the absence of the condition, while "1" indicates its presence. Significantly, when a feature's SHAP value is greater than 0, it suggests an increased risk of delirium, whereas a negative SHAP value suggests a reduced risk. GCS, Glasgow Coma Scale; MV, mechanical ventilation; APSIII, the Acute Physiology Score III.

providers identify delirium early in daily clinical practice and assist in medical decision-making.

Delirium is the most common neuropsychological complication during ICU stay for older patients. Delirium among older patients could lead to prolonged hospitalization day, increased mortality, and diminished long-term quality of life (5, 6, 8). Early recognition of risk factors related to delirium is important. The establishment of reliable delirium prediction models could assist clinicians in identifying high-risk patients and guiding timely intervention. Although several models have been developed to assess the risk of delirium in ICU, these models either encompass a wide range of age groups or solely focus on the recovery period after surgery, without considering the

specific characteristics of older patients in ICU settings (45–47). As far as we know, this is the first study on the risk prediction of delirium in critically ill patients aged 65 years and older. The best ML model selected in this study, namely XGBoost, showed good discrimination, calibration and clinical practicability in predicting the risk of delirium in ICU older patients. Recently, Marra et al. (14) developed a dynamic model to predict the risk of delirium in ICU patients. The model had a high negative predictive value (0.874) in excluding the next-day delirium, but a poor positive predictive value (0.548) and sensitivity (0.597). This suggests that the model is mainly used to exclude the risk of delirium, rather than identify high-risk patients (45). In contrast, our model not only has a high AUC value and accuracy, but also has good specificity, sensitivity, PPV, and NPV in both the training and validation sets. Therefore, it has higher clinical value in guiding targeted interventions to prevent older delirium in ICUs.

Feature selection is a crucial step in developing prediction models (48). Based on an extensive review of previously published literature on delirium risk factors, we have identified potential predictors of delirium and then comprehensively screened these risk factors from the database. It is noteworthy that we obtained a substantial sample size from the MIMIC-IV database, enabling us to incorporate a greater number of potential risk factors in our feature selection (37). This is crucial for identifying important predictive variables. We then utilized the LASSO regression to feature processing, which can avoid model overfitting and exclude the influence of strong collinearity related variables (49). In addition, the utilization of ML techniques to build prediction models can also easily handle multiple variables and capture nonlinear relationships (21). In the past, several studies have developed prediction models for delirium in the ICU. The PRE-DELIRIC and early PRE-DELIRIC model includes predictive variables such as age, illness severity score, patient classification, coma, use of sedatives and analgesics, and emergency admission; while the Lanzhou model incorporates mechanical ventilation, coma, blood urea nitrogen and mean arterial pressure at ICU admission, and medical history as predictive variables (12, 13, 15, 50). However, these models are built on traditional regression analysis methods with limited inclusion of population and candidate variables. They also target a broader age group and cannot reflect the specific characteristics of older patients. Our study focused on older ICU patients, as they are more to suffer from delirium (3). We extensively screened potential risk factors associated with critical delirium in older adults. We also found that the advanced age, severity score, use of sedation, type of admission and type of ICU, BUN, and mean BP was associated with the occurrence of delirium in older adults. In addition to these aforementioned risk factors, certain vital signs such as temperature, heart rate, respiratory rate, and SpO_2 also hold predictive value in our findings. These vital signs also reflect the severity of illness in critically ill older patients. Previous research has indicated that a history of conditions such as hypertension, chronic obstructive pulmonary disease, and diabetes is linked to the occurrence of delirium (6, 29). However, our findings suggest that certain comorbidities, including acute kidney injury, stroke, and atrial fibrillation, have a higher predictive value for the risk of delirium in older individuals. It is worth noting that the analysis results also found that marital status impacts delirium occurrence: married older patients had a lower risk of delirium in the prediction model. This aspect has received less attention in previous studies on non-older patients, possibly because marital status affects the emotional state of older patients, which in turn influences delirium occurrence (51, 52). Further research is needed to confirm this hypothesis.

The interpretability of ML has always been a challenging problem (18). To address this issue, we employed the SHAP values to analyze each feature and enhance the interpretability of the model (19). Based on the SHAP importance ranking, it is visually evident that the important features significantly influence the occurrence of delirium in older patients within ICUs. Notably, advanced age, low GCS score, high SOFA score, high APSIII score, MV treatment, and sedative use have all been widely reported as risk factors for delirium (6, 29, 31, 32). Recently, Zhang et al. (53) used ML methods to develop a prediction model for patients with sepsis-related delirium. The model successfully identified the top 10 important features impacting outcomes, including MV, initial ICU type, GCS, sedation, temperature, and age. This has high consistency with the predictive features obtained in our study. However, due to different study outcomes, there are discrepancies in the ranking of feature importance. Interestingly, we observed that there is a complex nonlinear correlation between GCS and the predicted outcome through the SHAP dependency plot, which has also been observed in other delirium prediction models (53). From a clinical perspective, a GCS score of 3 indicates severe brain damage, while a score of 15 suggests normal brain function. Therefore, patients in both groups had significantly reduced risk of developing delirium. Additionally, the use of SHAP force plots also provides personalized prediction insights for delirium, visually guiding clinicians and patients in decision-making. Taken together, the combination of XGBoost and SHAP can provide clear explanations for personalized risk prediction, facilitating an enhanced comprehension of the efficacy of important features within the model.

There are several limitations in this study. Firstly, not all patients in the database received CAM-ICU evaluation for delirium diagnosis, and this study excluded those who did not receive delirium assessment, which may lead to selection bias in the sample population. Secondly, despite our best efforts to collect potential predictors of delirium, some risk factors such as education level, alcohol consumption history, and activities of daily living were not recorded in the database, so we were unable to obtain this information. In fact, these factors may also have an impact on the occurrence of delirium after admission (29, 36). Also, several variables had to be excluded due to a high number of missing values. These may have caused us to overlook some features. Thirdly, we could not conduct further analysis on the potential effects of MV duration, types and doses of sedative drugs used in older adults within the ICU, which may potentially complicate our predictive variables for older delirium. Finally, the model has been validated and demonstrated excellent performance in the internal validation cohorts; however, it lacks external validation. While ML has the potential to improve clinical care by providing prediction for the risk of delirium in older adults, researchers should critically evaluate data sources, feature selection, and machine learning algorithms (20). In clinical practice, researchers should use an analysis framework that is consistent with the research objectives of this study, and conduct prospective cohort studies to verify the generalizability and reproducibility of results. Interdisciplinary research teams, including machine learning experts and clinical specialists, should work together to validate and evaluate prediction models. The interpretation of predictive outcomes should be more closely integrated with clinical practice in order to better improve patient care.

Conclusion

In summary, our study developed a ML model based on the MIMIC-IV v2.2 databases for early prediction of delirium risk in older ICU patients. The XGBoost model outperformed other models in terms of prediction performance. The SHAP methods were used to explain intrinsic information of the XGBoost model, which can provide clear explanations for personalized risk prediction and facilitate a more intuitive understanding of the effects of key features. These findings have the potential to assist clinicians in screening older patients at high risk of critical delirium and help optimize management strategies.

Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://mimic.mit.edu.

Ethics statement

The studies involving humans were approved by the Massachusetts Institute of Technology and the Beth Israel Deaconess Medical Center. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

DT: Data curation, Formal analysis, Investigation, Methodology, Software, Validation, Writing – original draft. CM: Conceptualization, Methodology, Project administration, Resources, Supervision, Writing – review & editing. YX: Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1399848/full#supplementary-material

References

1. Mattison MLP. Delirium. *Ann Intern Med*. (2020) 173:ITC49–64. doi: 10.7326/AITC202010060

2. Thom RP, Levy-Carrick NC, Bui M, Silbersweig D. Delirium. *Am J Psychiatry*. (2019) 176:785–93. doi: 10.1176/appi.ajp.2018.18070893

3. Stollings JL, Kotfis K, Chanques G, Pun BT, Pandharipande PP, Ely EW. Delirium in critical illness: clinical manifestations, outcomes, and management. *Intensive Care Med*. (2021) 47:1089–103. doi: 10.1007/s00134-021-06503-1

4. Fong TG, Tulebaev SR, Inouye SK. Delirium in elderly adults: diagnosis, prevention and treatment. *Nat Rev Neurol*. (2009) 5:210–20. doi: 10.1038/nrneurol.2009.24

5. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet*. (2014) 383:911–22. doi: 10.1016/S0140-6736(13)60688-1

6. Marcantonio ER. Delirium in hospitalized older adults. *N Engl J Med*. (2017) 377:1456–66. doi: 10.1056/NEJMcp1605501

7. Lin WL, Chen YF, Wang J. Factors associated with the development of delirium in elderly patients in intensive care units. *J Nurs Res*. (2015) 23:322–9. doi: 10.1097/JNR.0000000000000082

8. Wilcox ME, Girard TD, Hough CL. Delirium and long term cognition in critically ill patients. *BMJ*. (2021) 373:n1007. doi: 10.1136/bmj.n1007

9. Trogrlić Z, van der Jagt M, Bakker J, Balas MC, Ely EW, van der Voort PHJ, et al. A systematic review of implementation strategies for assessment, prevention, and management of ICU delirium and their effect on clinical outcomes. *Crit Care*. (2015) 19:157. doi: 10.1186/s13054-015-0886-9

10. Palakshappa JA, Hough CL. How we prevent and treat delirium in the ICU. *Chest*. (2021) 160:1326–34. doi: 10.1016/j.chest.2021.06.002

11. Devlin JW, Skrobik Y, Gélinas C, Needham DM, Slooter AJC, Pandharipande PP, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med*. (2018) 46:e825–73. doi: 10.1097/CCM.0000000000003299

12. van den Boogaard M, Schoonhoven L, Maseda E, Plowright C, Jones C, Luetz A, et al. Recalibration of the delirium prediction model for ICU patients (PRE-DELIRIC): a multinational observational study. *Intensive Care Med*. (2014) 40:361–9. doi: 10.1007/s00134-013-3202-7

13. Chen Y, Du H, Wei BH, Chang XN, Dong CM. Development and validation of risk-stratification delirium prediction model for critically ill patients: a prospective, observational, single-center study. *Medicine*. (2017) 96:e7543. doi: 10.1097/MD.0000000000007543

14. Marra A, Pandharipande PP, Shotwell MS, Chandrasekhar R, Girard TD, Shintani AK, et al. Acute Brain Dysfunction: Development and Validation of a Daily Prediction Model. *Chest*. (2018) 154:293–301. doi: 10.1016/j.chest.2018.03.013

15. van den Boogaard M, Pickkers P, Slooter AJ, Kuiper MA, Spronk PE, van der Voort PH, et al. Development and validation of PRE-DELIRIC (PREdiction of DELIRium in ICu patients) delirium prediction model for intensive care patients: observational multicentre study. *BMJ*. (2012) 344:e420. doi: 10.1136/bmj.e420

16. The Lancet Respiratory Medicine. Opening the black box of machine learning. *Lancet Respir Med*. (2018) 6:801. doi: 10.1016/S2213-2600(18)30425-9

17. Lundberg SM, Erion G, Chen H, DeGrave A, Prutkin JM, Nair B, et al. From local explanations to global understanding with explainable AI for trees. *Nat Mach Intell*. (2020) 2:56–67. doi: 10.1038/s42256-019-0138-9

18. Racine AM, Tommet D, D'Aquila ML. Machine Learning to Develop and Internally Validate a Predictive Model for Post-operative Delirium in a Prospective, Observational Clinical Cohort Study of Older Surgical Patients. *J Gen Intern Med*.. (2021) 36:265–273. doi: 10.1007/s11606-020-06238-7

19. Song Y, Zhang D, Wang Q, Liu Y, Chen K, Sun J, et al. Prediction models for postoperative delirium in elderly patients with machine-learning algorithms and SHapley additive exPlanations. *Transl Psychiatry*. (2024) 14:57.

20. Speiser JL, Callahan KE, Houston DK, Fanning J, Gill TM, Guralnik JM, et al. Machine learning in aging: an example of developing prediction models for serious fall injury in older adults. *J Gerontol A*. (2021) 76:647–54. doi: 10.1093/gerona/glaa138

21. Patton MJ, Liu VX. Predictive modeling using artificial intelligence and machine learning algorithms on electronic health record data: advantages and challenges. *Crit Care Clin*. (2023) 39:647–73. doi: 10.1016/j.ccc.2023.02.001

22. Lundberg SM, Nair B, Vavilala MS, Horibe M, Eisses MJ, Adams T, et al. Explainable machine-learning predictions for the prevention of hypoxaemia during surgery. *Nat Biomed Eng*. (2018) 2:749–60. doi: 10.1038/s41551-018-0304-0

23. Hu C, Tan Q, Zhang Q, Li Y, Wang F, Zou X, et al. Application of interpretable machine learning for early prediction of prognosis in acute kidney injury. *Comput Struct Biotechnol J*. (2022) 20:2861–70. doi: 10.1016/j.csbj.2022.06.003

24. Jiang Z, Bo L, Wang L, Xie Y, Cao J, Yao Y, et al. Interpretable machine-learning model for real-time, clustered risk factor analysis of sepsis and septic death in critical care. *Comput Methods Prog Biomed*. (2023) 241:107772. doi: 10.1016/j.cmpb.2023.107772

25. Johnson AE, Pollard TJ, Shen L, Lehman LW, Feng M, Ghassemi M, et al. MIMIC-III, a freely accessible critical care database. *Sci Data*. (2016) 3:160035. doi: 10.1038/sdata.2016.35

26. Johnson AEW, Bulgarelli L, Shen L, Gayles A, Shammout A, Horng S, et al. MIMIC-IV, a freely accessible electronic health record dataset. *Sci Data*. (2023) 10:1. doi: 10.1038/s41597-022-01899-x

27. Collins GS, Reitsma JB, Altman DG, Moons KGM. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): the TRIPOD statement. *BMJ*. (2015) 350:g7594. doi: 10.1136/bmj.g7594

28. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, et al. Evaluation of delirium in critically ill patients: validation of the confusion assessment method for the intensive care unit (CAM-ICU). *Crit Care Med*. (2001) 29:1370–9. doi: 10.1097/00003246-200107000-00012

29. Cortés-Beringola A, Vicent L, Martín-Asenjo R, Puerto E, Domínguez-Pérez L, Maruri R, et al. Diagnosis, prevention, and management of delirium in the intensive cardiac care unit. *Am Heart J*. (2021) 232:164–76. doi: 10.1016/j.ahj.2020.11.011

30. Guo R, Zhang S, Yu S, Li X, Liu X, Shen Y, et al. Inclusion of frailty improved performance of delirium prediction for elderly patients in the cardiac intensive care unit (D-FRAIL): a prospective derivation and external validation study. *Int J Nurs Stud*. (2023) 147:104582. doi: 10.1016/j.ijnurstu.2023.104582

31. Choi NY, Kim EH, Baek CH, Sohn I, Yeon S, Chung MK. Development of a nomogram for predicting the probability of postoperative delirium in patients undergoing free flap reconstruction for head and neck cancer. *Eur J Surg Oncol*. (2017) 43:683–8. doi: 10.1016/j.ejso.2016.09.018

32. Bramley P, McArthur K, Blayney A, McCullagh I. Risk factors for postoperative delirium: an umbrella review of systematic reviews. *Int J Surg*. (2021) 93:106063. doi: 10.1016/j.ijsu.2021.106063

33. Zaal IJ, Devlin JW, Peelen LM, Slooter AJC. A systematic review of risk factors for delirium in the ICU. *Crit Care Med*. (2015) 43:40–7. doi: 10.1097/CCM.0000000000000625

34. Gao L, Gaba A, Li P, Saxena R, Scheer FAJL, Akeju O, et al. Heart rate response and recovery during exercise predict future delirium risk-a prospective cohort study in middle- to older-aged adults. *J Sport Health Sci*. (2023) 12:312–23. doi: 10.1016/j.jshs.2021.12.002

35. Monte R, Rabuñal R, Casariego E, Bal M, Pértega S. Risk factors for delirium tremens in patients with alcohol withdrawal syndrome in a hospital setting. *Eur J Intern Med*. (2009) 20:690–4. doi: 10.1016/j.ejim.2009.07.008

36. Pun BT, Badenes R, Heras la Calle G, Orun OM, Chen W, Raman R, et al. Prevalence and risk factors for delirium in critically ill patients with COVID-19 (COVID-D): a multicentre cohort study. *Lancet Respir Med*. (2021) 9:239–50. doi: 10.1016/S2213-2600(20)30552-X

37. Riley RD, Ensor J, Snell KIE, Harrell FE Jr, Martin GP, Reitsma JB, et al. Calculating the sample size required for developing a clinical prediction model. *BMJ*. (2020) 368:m441. doi: 10.1136/bmj.m441

38. Peduzzi P, Concato J, Kemper E, Holford TR, Feinstein AR. A simulation study of the number of events per variable in logistic regression analysis. *J Clin Epidemiol*. (1996) 49:1373–9. doi: 10.1016/S0895-4356(96)00236-3

39. Ma C, Sun GR, Yang XW, Yang S. A clinically applicable prediction model for the risk of in-hospital mortality in solid cancer patients admitted to intensive care units with sepsis. *J Cancer Res Clin Oncol*. (2023) 149:7175–85. doi: 10.1007/s00432-023-04661-x

40. Faquih T, van Smeden M, Luo J, Le Cessie S, Kastenmüller G, Krumsiek J, et al. A workflow for missing values imputation of untargeted metabolomics data. *Metabolites*. (2020) 10:486. doi: 10.3390/metabo10120486

41. Sun K, Huang SH, Wong DSH, Jang SS. Design and application of a variable selection method for multilayer perceptron neural network with LASSO. *IEEE Trans Neural Netw Learn Syst*. (2017) 28:1386–96. doi: 10.1109/TNNLS.2016.2542866

42. Guan C, Ma F, Chang S, Zhang J. Interpretable machine learning models for predicting venous thromboembolism in the intensive care unit: an analysis based on data from 207 centers. *Crit Care*. (2023) 27:406. doi: 10.1186/s13054-023-04683-4

43. Zhou S, Lu Z, Liu Y, Wang M, Zhou W, Cui X, et al. Interpretable machine learning model for early prediction of 28-day mortality in ICU patients with sepsis-induced coagulopathy: development and validation. *Eur J Med Res*. (2024) 29:14. doi: 10.1186/s40001-023-01593-7

44. Hu C, Gao C, Li T, Liu C, Peng Z. Explainable artificial intelligence model for mortality risk prediction in the intensive care unit: a derivation and validation study. *Postgrad Med J*. (2024) 100:219–27. doi: 10.1093/postmj/qgad144

45. Green C, Bonavia W, Toh C, Tiruvoipati R. Prediction of ICU delirium: validation of current delirium predictive models in routine clinical practice. *Crit Care Med*. (2019) 47:428–35. doi: 10.1097/CCM.0000000000003577

46. Song YX, Yang XD, Luo YG, Ouyang CL, Yu Y, Ma YL, et al. Comparison of logistic regression and machine learning methods for predicting postoperative delirium in elderly patients: a retrospective study. *CNS Neurosci Ther*. (2023) 29:158–67. doi: 10.1111/cns.13991

47. Wassenaar A, Schoonhoven L, Devlin JW, van Haren FMP, Slooter AJC, Jorens PG, et al. Delirium prediction in the intensive care unit: comparison of two delirium prediction models. *Crit Care*. (2018) 22:114. doi: 10.1186/s13054-018-2037-6

48. Chowdhury MZI, Turin TC. Variable selection strategies and its importance in clinical prediction modelling. *Fam Med Community Health*. (2020) 8:e000262. doi: 10.1136/fmch-2019-000262

49. Tibshirani R. The lasso method for variable selection in the Cox model. *Stat Med*. (1997) 16:385–95. doi: 10.1002/(SICI)1097-0258(19970228)16:4<385::AID-SIM380>3.0.CO;2-3

50. Wassenaar A, van den Boogaard M, van Achterberg T, Slooter AJC, Kuiper MA, Hoogendoorn ME, et al. Multinational development and validation of an early prediction model for delirium in ICU patients. *Intensive Care Med*. (2015) 41:1048–56. doi: 10.1007/s00134-015-3777-2

51. Andrews PS, Thompson J, Raman R, Rick C, Kiehl A, Pandharipande P, et al. Delirium, depression, and long-term cognition. *Int Psychogeriatr*. (2023) 35:433–8. doi: 10.1017/S1041610221002556

52. Bulloch AGM, Williams JVA, Lavorato DH, Patten SB. The depression and marital status relationship is modified by both age and gender. *J Affect Disord*. (2017) 223:65–8. doi: 10.1016/j.jad.2017.06.007

53. Zhang Y, Hu J, Hua T, Zhang J, Zhang Z, Yang M. Development of a machine learning-based prediction model for sepsis-associated delirium in the intensive care unit. *Sci Rep*. (2023) 13:12697. doi: 10.1038/s41598-023-38650-4

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Frailty index and risk of delirium in hospitalized patients: a two-sample Mendelian randomization study

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Objective: Observational studies suggest that the frailty index (FI) is closely related to delirium, but the relationship between them is still uncertain due to the influence of various confounding factors. Therefore, two-sample Mendelian randomization (MR) was used to explore the causal relationship between the FI and delirium risk.

Methods: This study obtained pooled statistics for the FI and delirium from two of the most extensive genome-wide association studies. To make the results more robust and reliable, supplementary analyses were performed using several robust analytical methods (inverse-variance weighting, MR-Egger regression, and weighted median). In addition, this study used the MR-Egger intercept test, Cochran's Q test, funnel plots and the leave-one-out method to evaluate the pleiotropy and heterogeneity among the abovementioned genetic variation instrumental variables.

Results: Frailty might increase the relative risk of delirium, as shown by IVW (OR = 1.849, 95% CI 0.027∼2.067, P = 0.044), weighted median (OR = 1.726, 95% CI −0.178∼2.664, P = 0.083), MR-Egger regression (OR = 1.768, 95% CI −3.08∼6.171, P = 0.525) and leave-one-out sensitivity analysis (P = 0.058). Although the WME method and MR–Egger regression analysis showed no statistically significant causal relationship between the FI and the risk of delirium, the direction of the causal effect was consistent with the IVW method.

Conclusion: There is a notable correlation between a higher FI and an elevated risk of delirium. This indicates that healthcare providers should take proactive measures to prevent delirium in hospitalized patients with a higher FI.

KEYWORDS

frailty index, delirium, Mendelian randomization study, intensive care, nursing care

Relevance statement

With the arrival of an aging society, frailty has received increasing attention in clinical nursing work, and previous observational studies have shown that frailty can increase the incidence of delirium, leading to poor prognosis. Both frailty and delirium are complications that require attention in daily nursing work. Therefore, this study intends to use Mendelian randomization method to explore the causal relationship between frailty and delirium, thereby providing a theory for improving the quality of clinical nursing care.

1 Background

Delirium, a profound and sudden-onset neuropsychiatric condition, is distinguished by compromised focus and awareness, an ever-changing trajectory, and general cognitive decline (1). Greatly prevalent among the elderly and critically ill, this syndrome has numerous predisposing factors and frequently manifests as a complication of sudden illness, substance overconsumption or cessation, surgical intervention, or disturbances in electrolyte or metabolic levels; it can even arise solely due to hospitalization (2). Despite the high frequency of delirium cases, its identification, diagnosis, and treatment in clinical practice are often neglected, misjudged, or inadequately handled.

Observational studies conducted in Italy aimed to examine the potential association between frailty and delirium in hospitalized older adults and in different contexts (3), and others were investigated the impact of these syndromes on outcomes including maintaining attention, functional status and mortality (4, 5). Different researchers also conducted systematic reviews and meta-analyses of the literature to address this issue, showing that frailty and delirium are common in geriatric practice, but their association with each other and their effect on short-term mortality in the general population hospitalized for acute conditions remains largely unknown (6, 7). The findings of this study suggest that frailty is indeed associated with delirium in hospitalized elderly patients. Furthermore, the presence of both conditions, either alone or in combination, leads to increased short-term mortality rates.

Notably, the connection between frailty and delirium is frequently assessed through observation-based studies. The currently debated aspect of the frailty-delirium relationship stems from the biases, confounding factors, and constraints inherent in observational studies. The utilization of Mendelian randomization (MR) provides a robust method for identifying causal links between risk factors and diseases by leveraging genetic variation as an instrumental variable (8). Given that genetic variation is determined at conception, it is generally less susceptible to external factors. Additionally, MR research mitigates concerns surrounding the causal sequence, a critical aspect of causal inference and the foundation of establishing causality (9). Hence, this study incorporates a two-sample MR analysis utilizing publicly available data from genome-wide association studies (GWAS) to investigate the causal association between the FI and the susceptibility to delirium.

TABLE 1 Basic information of each SNP in the FI and delirium databases.

SNP	Chr	EA	OA	EAF	FI			Delirium		
					Beta	SE	*P*-value	Beta	SE	*P*-value
rs10891490	11	C	T	0.5915	−0.0188	0.0034	2.00E-08	−.0369	0.042	0.3795
rs12739243	1	C	T	0.2206	−0.0242	0.004	1.28E-09	−0.07	0.044	0.1113
rs1363103	5	C	T	0.38	−0.0191	0.0034	2.23E-08	0.0115	0.0413	0.781601
rs17612102	15	C	T	0.5933	0.0187	0.0034	2.85E-08	−0.0103	0.0408	0.7997
rs2071207	3	C	T	0.478	−0.0187	0.0033	1.47E-08	−0.0832	0.0403	0.03886
rs2396766	7	A	G	0.4725	0.0201	0.0033	1.22E-09	−0.0444	0.0403	0.2708
rs3959554	15	G	A	0.4177	0.0189	0.0034	1.74E-08	0.0406	0.0431	0.3457
rs4146140	10	T	C	0.3811	−0.0198	0.0034	6.83E-09	0.0161	0.0427	0.7065
rs4952693	2	T	C	0.3734	−0.0194	0.0034	1.47E-08	−0.0241	0.0409	0.555699
rs56299474	8	A	C	0.1733	0.0241	0.0044	3.94E-08	−0.0235	0.0548	0.667599
rs583514	3	C	T	0.5111	0.0199	0.0033	1.65E-09	0.0609	0.0405	0.1321
rs8089807	18	T	C	0.1866	−0.0248	0.0043	6.50E-09	−0.0692	0.0573	0.2266
rs82334	4	C	A	0.3177	−0.0223	0.0035	3.13E-10	0.0063	0.0406	0.8761
rs9275160	6	A	G	0.3397	0.0382	0.0035	7.18E-28	0.0475	0.0443	0.2842

SNP, single-nucleotide polymorphisms; Chr, chromosome; EA, effect_allele; OA, other_allele; EAF, effect allele frequency.

TABLE 2 Instrumental variable test in the causal analysis of the FI and delirium.

Exposure variable	Number of instrumental variables	F value		MR-Egger regression		Leave-one-out sensitivity analysis
		Max	Min	Intercept	*P*-value	*P*-value
Frailty index	14	30	119.1	−0.011	0.832	0.058

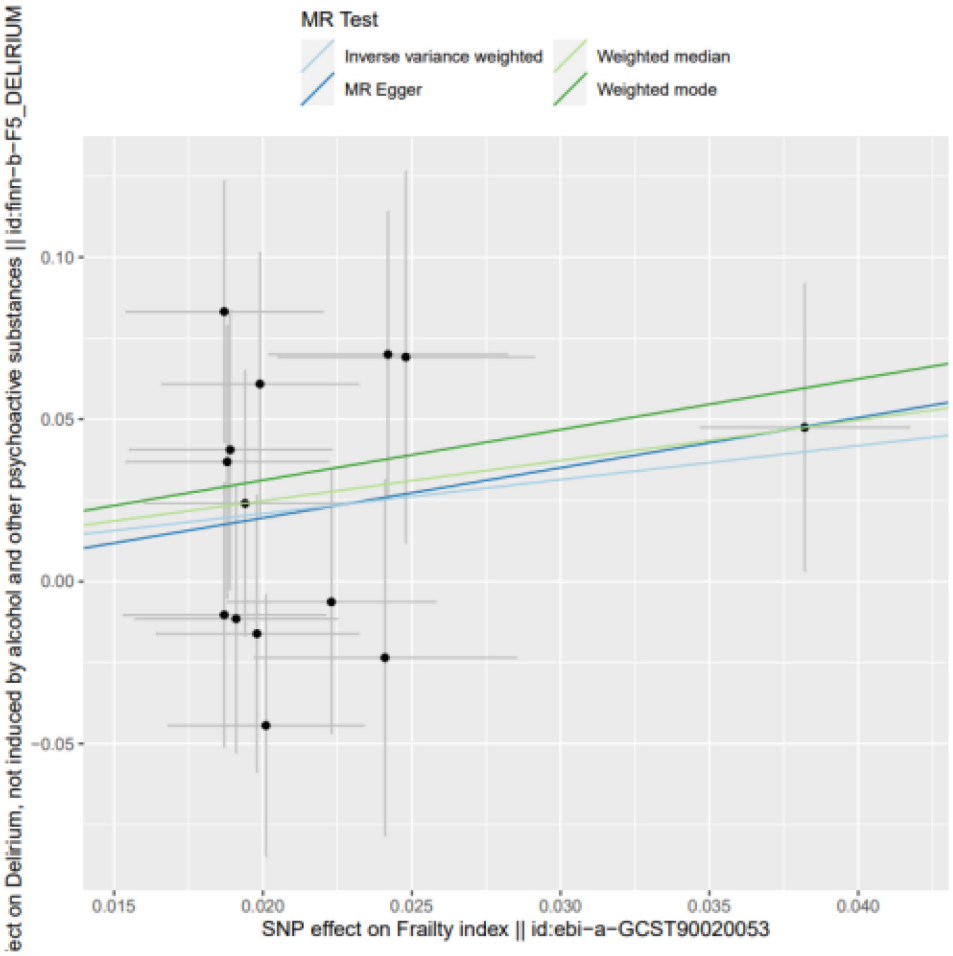

FIGURE 1
SNP effects on the outcome against SNP effects on the exposure. Frailty might increase the relative risk of delirium, as demonstrated by IVW (OR = 1.849, 95% CI 0.027~2.067, P = 0.044), the weighted median (OR = 1.726, 95% CI −0.178~2.664, P = 0.083) and MR-Egger regression (OR = 1.768, 95% CI −3.08~6.171, P = 0.525).

2 Materials and methods

2.1 Design

To assess whether there is a causal relationship between frailty and delirium, a two-sample MR was used in this study.

2.2 Data sources

For the purpose of this analysis, single-nucleotide polymorphisms (SNPs) associated with the FI were obtained from the European Bioinformatics Institute (EBI) as instrumental variables. The working variable (ID: ebi-a-GCST90020053) originates from a Genome-wide association study (GWAS) on frailty (10), which included 164,610 samples of individuals aged 60 to 70 years. The sample population consisted of 84,819 females (51.3%), the detail information is in the **Supplementary Table 1**. The relevant SNP data on delirium was obtained from the Finnish database. This dataset mainly comes from the European population, contains a total of 16,380,452 SNPs and the inclusion criteria were acute or subacute: (1) brain syndrome; (2) confusional state (nonalcoholic); (3) infective psychosis; (4) organic reaction; (5) psycho-organic syndrome. Delirium cases were excluded if they were described as delirium tremens, alcohol-induced, or unspecified. Delirium was diagnosed based on the patient's ICD-10 code at discharge, and the database did not specify which delirium assessment scale was used to assess the patient during the hospitalization. And the detail basal information of delirium datasets is in the **Supplementary Table 2** and **Supplementary Figures 1, 2**.

2.3 Selection of instrumental variables

First, this study used Plink software to screen out SNPs with $P < 5 \times 10^{-8}$, a genetic distance of 10,000 kb and linkage disequilibrium (LD) $r^2 < 0.001$ from the FI database (11). Second, the catalog and PhenoScanner databases were also used to further verify whether the above included SNPs were related to other confounding factors (12). Finally, the F statistic was used to evaluate whether the included SNPs were affected by weak instrumental

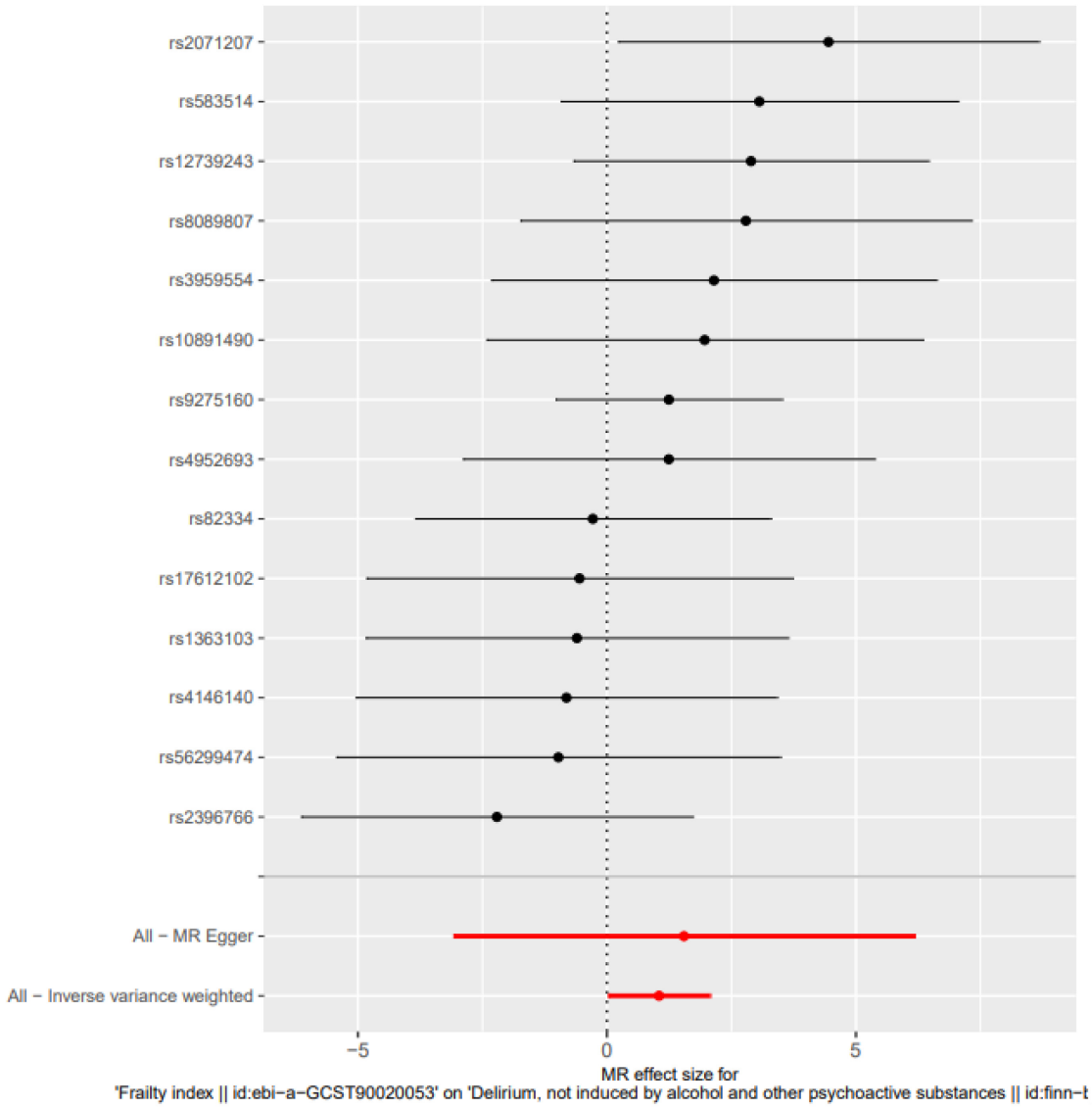

FIGURE 2
Single SNP analysis. The Single SNP analysis showed IVW (OR = 1.849, 95% CI 0.027~2.067, P = 0.044), and MR-Egger regression (OR = 1.768, 95% CI −3.08~6.171, P = 0.525).

variables (13). If the F statistic of SNPs is less than 10, it indicates that there is a possibility of weak instrumental variable bias in the SNPs, and then it will be eliminated to avoid affecting the results.

2.4 Statistics

This study mainly used the inverse-variance weighted (IVW) method, wherein the existence of the intercept item is not considered in the regression and the reciprocal of the outcome variance is used as the weight for fitting (14). Among the different IVW approaches, the IVW fixed-effects model was mainly used in the absence of any underlying heterogeneity of horizontal pleiotropic effects. If heterogeneity existed, a random-effects model was used. Second, this study used methods such as MR-Egger regression and the weighted median estimator (WME) to further supplement the above conclusions. The biggest difference between the MR-Egger method and the IVW method is that the existence of the intercept item is considered in the MR–Egger regression, and it also uses the reciprocal of the outcome variance as the weight for fitting (15). The weighted median method was defined as the median of the weighted empirical density function of ratio estimates, from which causality was assessed if at least 50% of the information in the analysis came from valid tools.

2.5 Analyses of horizontal pleiotropy and heterogeneity

This study used the "leave-one-out" sensitivity analysis by removing individual SNPs one-at-a-time to assess whether that variation drove the association between exposure and outcome variables. Second, to clarify whether there was horizontal pleiotropy in the MR analysis, this study also carried out MR-Egger intercept

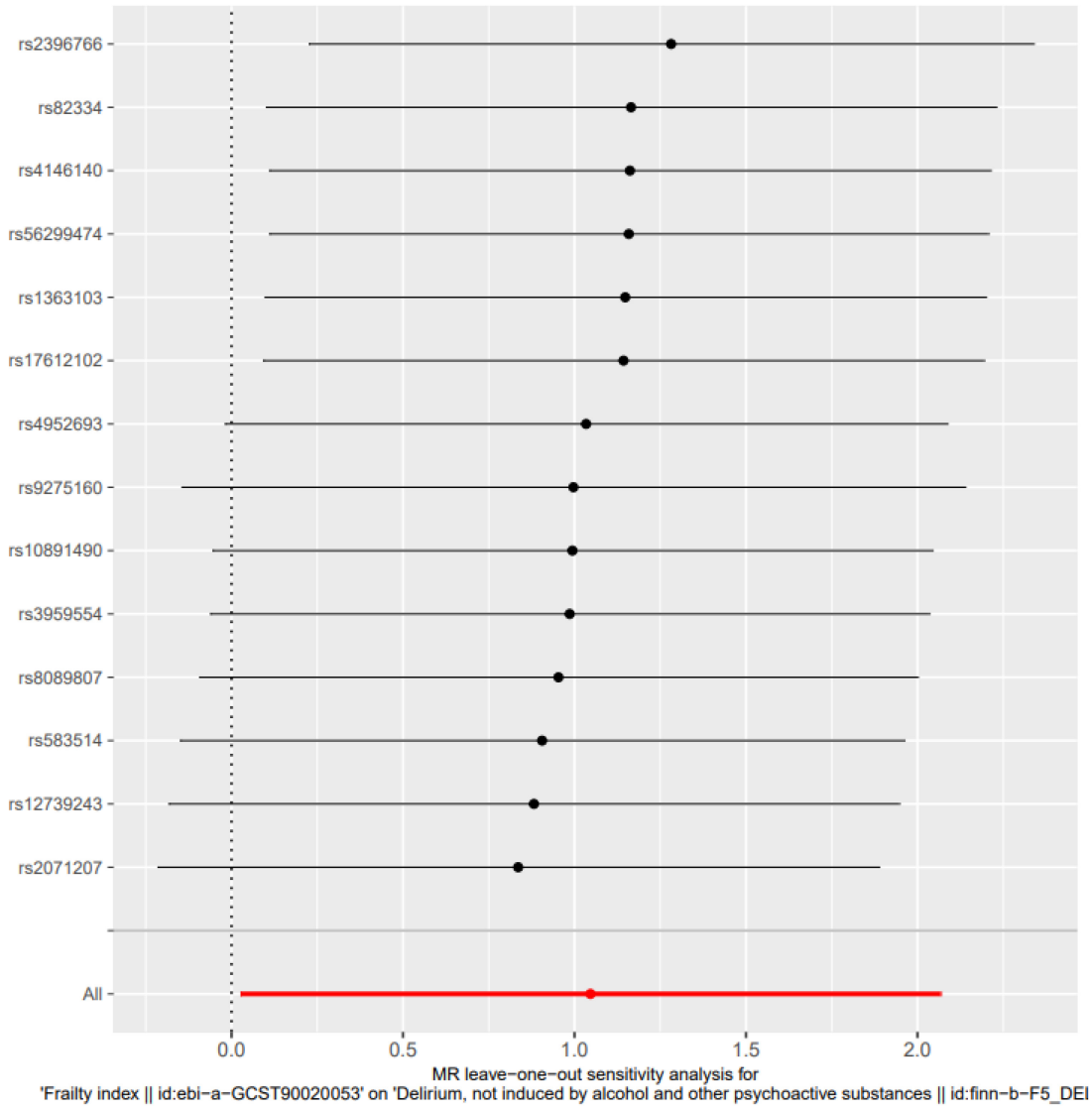

FIGURE 3
Leave-one-out sensitivity analysis. The "leave-one-out" sensitivity analysis showed that the included SNPs had no significant impact on the results (P = 0.058).

detection. If the intercept item in the MR–Egger intercept analysis had obvious statistical significance, then it indicated that the study had obvious significance. Finally, this study also used Cochran's Q statistic to detect heterogeneity. Significant heterogeneity in the results of the analysis was demonstrated if the Cochran's Q test result was statistically significant. $P < 0.05$ was considered to indicate statistical significance. All statistical analyses were performed using R program (version 4.2.0), including packages such as TwoSampleMR.

3 Results

3.1 Selection of instrumental variables

In this study, 14 genome-wide significant SNPs closely related to frailty were selected as instrumental variables (see Table 1). The included SNPs explained approximately 7.41% of the phenotypic variation, and the F values of the included SNPs were all greater than 10, which proved that the study was not easily affected by weak instrumental variables. The MR-Egger regression intercept and leave-one-out sensitivity analysis showed no horizontal pleiotropy for any instrumental variable (see Table 2).

3.2 Estimation results of the MR method

Frailty might increase the relative risk of delirium, as demonstrated by IVW (OR = 1.849, 95% CI 0.027∼2.067, P = 0.044), the weighted median (OR = 1.726, 95% CI −0.178∼2.664, P = 0.083) and MR-Egger regression (OR = 1.768, 95% CI −3.08∼6.171, P = 0.525). Although the WME method and MR–Egger regression analysis showed no statistically significant causal relationship between the FI and the risk of delirium, the

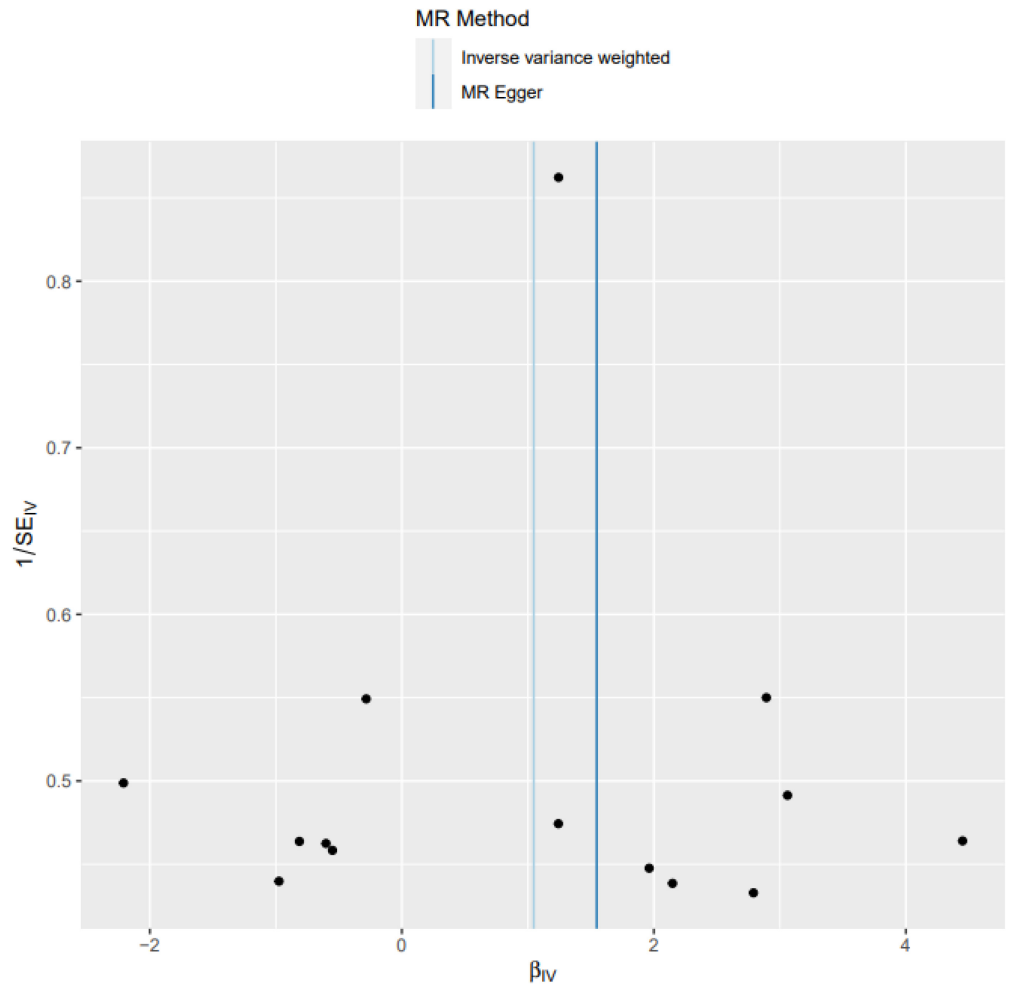

FIGURE 4
Funnel plot. The funnel plot also showed that the included SNPs had no significant impact on the results.

direction of the causal effect was consistent with the IVW method (see Figures 1, 2).

3.3 Horizontal pleiotropic and heterogeneity analysis

MR-Egger intercept analysis showed that there was no horizontal pleiotropic effect in this study (P = 0.832). Second, Cochran's Q test showed that there was no certain heterogeneity in the study results (P = 0.583), and the "leave-one-out" sensitivity analysis and funnel plot also showed that the included SNPs had no significant impact on the results (see Figures 3, 4).

4 Discussion

This scientific investigation employed a Mendelian randomization analysis using a two-sample approach to evaluate the causality between the FI and the likelihood of experiencing delirium. The study uncovered a potential exacerbating impact of frailty on the risk of delirium in hospitalized patients, providing a basis for establishing a causal relationship between frailty and delirium. Delirium, characterized by impaired attention and confusion, represents a frequently encountered complication among hospitalized individuals, particularly among the elderly The occurrence of delirium can ascend to as high as 60%. A pharmacoepidemiological study was to describe the pattern of use of antidepressant medication the elderly population. Meantime, pharmacological treatment of delirium is receiving increasing attention (16). Concurrently, frailty is highly prevalent among elderly patients admitted to hospitals. Nonetheless, the presence of a causal association between these two phenomena remains ambiguous. The significance of the link between frailty and delirium warrants discussion. Despite the seemingly intuitive nature of this relationship, the current body of literature providing evidence for it is lacking, with most studies focusing on surgical contexts (17–19). And the relevant relationship between frailty and cardiovascular diseases and sarcopenia were also got the same results (20, 21). To shed light on this matter, Zhang et al. (6) executed a meta-analysis in 2021 exploring the interplay between frailty and delirium. The analysis divulged that the incidence of delirium in frail hospitalized patients was approximately three times higher compared to their non-frail counterparts (6). It is

essential to consider, however, that the majority of studies included in the meta-analysis were of an observational nature, engendering a high level of heterogeneity among the included studies, thus limiting the ability to definitively establish a causal connection between frailty and delirium. A single-center study examined the impact of frailty and delirium on patient survival, revealing that frail individuals with delirium faced a higher long-term mortality risk compared to those who were fit (22). This finding aligns with the current study's results and with previous research highlighting the significant influence of frailty on mortality (23, 24).

Our study possesses various strengths in contrast to observational studies. Firstly, we employed a comprehensive large-sample genome-wide association study, enabling a thorough analysis of delirium events. Secondly, we utilized several alternative methods that produced consistent results. However, it is crucial to exercise caution when interpreting these findings as certain limitations exist. Initially, the MR study employed GWAS data sourced exclusively from the European population, necessitating further studies to determine the generalizability of our research to other populations. Additionally, our study employed three statistical methods, with only the IVW method yielding statistically significant results. This may possibly be attributed to the fact that our study only included European population, leading to reduced statistical power in the causality assessment. Hence, it is imperative to conduct additional causality assessments encompassing diverse racial backgrounds in order to attain more reliable conclusions.

In conclusion, this study is the first to comprehensively explore the causal relationship between the FI and the risk of delirium in hospitalized patients through two-sample MR analysis. The results showed that there was a notable correlation between a higher FI and an elevated risk of delirium. This indicates that healthcare providers should take proactive measures to prevent delirium in hospitalized patients with a higher FI.

Data availability statement

The datasets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found below: https://www.ebi.ac.uk/metagenomics/,ebi-a-GCST90020053.

Ethics statement

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent from the patients/participants or patients/participants legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

YC: Writing – original draft, Writing – review & editing. FF: Funding acquisition, Writing – review & editing. QL: Methodology, Resources, Writing – review & editing. HG: Software, Writing – review & editing. LZ: Software, Writing – review & editing. JL: Conceptualization, Supervision, Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2024.1361437/full#supplementary-material

SUPPLEMENTARY TABLE 1
The detail information of frailty datasets.

SUPPLEMENTARY TABLE 2
The detail basal information of delirium datasets.

SUPPLEMENTARY FIGURE 1
Survival analyses between endpoints of delirium datasets.

SUPPLEMENTARY FIGURE 2
Cumulative incidence of delirium.

References

1. Patnode CD, Henderson JT, Melnikow J, Coppola EL, Durbin S, Thomas RUS. *Preventive Services task force evidence syntheses, formerly systematic evidence reviews. Interventions for Tobacco cessation in adults, including pregnant women: An evidence update for the US preventive services task force*. Rockville, MD: Agency for Healthcare Research and Quality (US) (2021).

2. Faulkner KM, Uchmanowicz I, Lisiak M, Cichoń E, Cyrkot T, Szczepanowski R. Cognition and frailty in patients with heart failure: A systematic review of the association between frailty and cognitive impairment. *Front Psychiatry.* (2021) 12:713386. doi: 10.3389/fpsyt.2021.713386

3. Mazzola P, Tassistro E, Di Santo S, Rossi E, Andreano A, Valsecchi MG, et al. The relationship between frailty and delirium: Insights from the 2017 delirium day study. *Age Ageing.* (2021) 50:1593–9. doi: 10.1093/ageing/afab042

4. Bellelli PG, Biotto M, Morandi A, Meagher D, Cesari M, Mazzola P, et al. The relationship among frailty, delirium and attentional tests to detect delirium: A cohort study. *Eur J Intern Med.* (2019) 70:33–8. doi: 10.1016/j.ejim.2019.09.008

5. Gandossi CM, Zambon A, Oliveri G, Codognola M, Szabo H, Cazzulani I, et al. Frailty, post-operative delirium and functional status at discharge in patients with hip fracture. *Int J Geriatr Psychiatry.* (2021) 36:1524–30.

6. Zhang XM, Jiao J, Xie XH, Wu XJ. The association between frailty and delirium among hospitalized patients: An updated meta-analysis. *J Am Med Dir Assoc.* (2021) 22:527–34.

7. Persico I, Cesari M, Morandi A, Haas J, Mazzola P, Zambon A, et al. Frailty and delirium in older adults: A systematic review and meta-analysis of the literature. *J Am Geriatr Soc.* (2018) 66:2022–30.

8. Cai J, He L, Wang H, Rong X, Chen M, Shen Q, et al. Genetic liability for prescription opioid use and risk of cardiovascular diseases: A multivariable Mendelian randomization study. *Addiction.* (2022) 117:1382–91. doi: 10.1111/add.15767

9. Verbanck M, Chen CY, Neale B, Do R. Detection of widespread horizontal pleiotropy in causal relationships inferred from Mendelian randomization between complex traits and diseases. *Nat Genet.* (2018) 50:693–8.

10. Atkins JL, Jylhävä J, Pedersen NL, Magnusson PK, Lu Y, Wang Y, et al. A genome-wide association study of the frailty index highlights brain pathways in ageing. *Aging Cell.* (2021) 20:e13459. doi: 10.1111/acel.13459

11. Skrivankova VW, Richmond RC, Woolf BAR, Yarmolinsky J, Davies NM, Swanson SA, et al. Strengthening the reporting of observational studies in epidemiology using Mendelian randomization: The STROBE-MR statement. *JAMA.* (2021) 326:1614–21. doi: 10.1001/jama.2021.18236

12. Kamat MA, Blackshaw JA, Young R, Surendran P, Burgess S, Danesh J, et al. PhenoScanner V2: An expanded tool for searching human genotype-phenotype associations. *Bioinformatics.* (2019) 35:4851–3. doi: 10.1093/bioinformatics/btz469

13. Burgess S, Thompson SG. Avoiding bias from weak instruments in Mendelian randomization studies. *Int J Epidemiol.* (2011) 40:755–64.

14. Boef AG, Dekkers OM, le Cessie S. Mendelian randomization studies: A review of the approaches used and the quality of reporting. *Int J Epidemiol.* (2015) 44:496–511.

15. Burgess S, Thompson SG. Interpreting findings from Mendelian randomization using the MR-Egger method. *Eur J Epidemiol.* (2017) 32:377–89.

16. Giovannini S, Onder G, van der Roest HG, Topinkova E, Gindin J, Cipriani MC, et al. Use of antidepressant medications among older adults in European long-term care facilities: A cross-sectional analysis from the SHELTER study. *BMC Geriatr.* (2020) 20:310. doi: 10.1186/s12877-020-01730-5

17. Yamanashi T, Iwata M, Crutchley KJ, Sullivan EJ, Malicoat JR, Anderson ZM, et al. New cutoff scores for delirium screening tools to predict patient mortality. *J Am Geriatr Soc.* (2021) 69:140–7.

18. Basinski JR, Alfano CM, Katon WJ, Syrjala KL, Fann JR. Impact of delirium on distress, health-related quality of life, and cognition 6 months and 1 year after hematopoietic cell transplant. *Biol Blood Marrow Transplant.* (2010) 16:824–31. doi: 10.1016/j.bbmt.2010.01.003

19. Mahanna-Gabrielli E, Zhang K, Sieber FE, Lin HM, Liu X, Sewell M, et al. Frailty is associated with postoperative delirium but not with postoperative cognitive decline in older noncardiac surgery patients. *Anesth Analg.* (2020) 130:1516–23.

20. Giovannini S, Brau F, Forino R, Berti A, D'Ignazio F, Loreti C, et al. Sarcopenia: Diagnosis and management, state of the art and contribution of ultrasound. *J Clin Med.* (2021) 10:5552. doi: 10.3390/jcm10235552

21. Liperoti R, Vetrano DL, Palmer K, Targowski T, Cipriani MC, Lo Monaco MR, et al. Association between frailty and ischemic heart disease: A systematic review and meta-analysis. *BMC Geriatr.* (2021) 21:357. doi: 10.1186/s12877-021-02304-9

22. Eeles EM, White SV, O'Mahony SM, Bayer AJ, Hubbard RE. The impact of frailty and delirium on mortality in older inpatients. *Age Ageing.* (2012) 41:412–6.

23. Clegg A, Bates C, Young J, Ryan R, Nichols L, Ann Teale E, et al. Development and validation of an electronic frailty index using routine primary care electronic health record data. *Age Ageing.* (2016) 45:353–60.

24. Gilbert T, Neuburger J, Kraindler J, Keeble E, Smith P, Ariti C, et al. Development and validation of a hospital frailty risk score focusing on older people in acute care settings using electronic hospital records: An observational study. *Lancet.* (2018) 391:1775–82.

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Associations of serum lactate and lactate clearance with delirium in the early stage of ICU: a retrospective cohort study of the MIMIC-IV database

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Aim: This study aimed to investigate the associations of serum lactate level [within and after 24 h of the intensive care unit (ICU) admission] and lactate clearance rate with delirium and assess associations of lactate and lactate clearance rate with 30-day mortality in delirium patients.

Methods: Data in this retrospective cohort study were extracted from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database in 2012–2019. The associations of lactate and lactate clearance rate with delirium were explored through univariable and multivariable logistic regression analyses, whereas the associations of lactate and lactate clearance rate with 30-day mortality in delirium patients were investigated using univariable and multivariable Cox regression analyses. Subgroup analysis was performed for age, gender, sepsis, hypertension, sedative drug, ventilation, antibiotic drug, vasopressors, and the Sequential Organ Failure Assessment (SOFA) score. The evaluation indexes were odds ratios (ORs), hazard ratios (HRs), and 95% confidence intervals (CIs).

Results: Among 7,812 (14.58%) eligible participants, 4,338 (8.19%) had delirium and 1,903 (24.36%) died within 30 days. After adjusting for covariates, patients with lactic acidosis (lactate level > 5 mmol/L and PH < 7.35) at T0 (within 24 h of the ICU admission) had higher odds of delirium (OR = 1.235, 95%CI: 1.105–1.382). Hyperlactatemia (lactate level 2–5 mmol/L and PH > 7.35) at T1 (after 24 h of the ICU admission) was also associated with higher odds of delirium (OR = 1.277, 95%CI: 1.126–1.447). Lactate clearance rate > 50% was linked to lower odds of delirium (OR = 0.705, 95%CI: 0.613–0.811), and this relationship was also observed in ≥65 years old, female, male, non-sepsis, sepsis, non-hypertension, non-sedative drug use, sedative drug use, ventilation, antibiotic drug use, use of vasopressors, and different SOFA score subgroups (all $p < 0.05$). Additionally, hyperlactatemia and lactic acidosis (whether at T0 or T1) may be potential risk factors for 30-day mortality in delirium patients, whereas lactate clearance rate ≥ 0 had a potential protective effect on 30-day mortality (all $p < 0.05$).

Conclusion: Higher serum lactate levels in the early stage of the ICU were associated with a higher risk of delirium and subsequent mortality. Measures taken to increase the lactate clearance rate are necessary to reduce potential delirium or mortality risk in clinical settings. However, more evidence from prospective studies is needed to verify these findings.

KEYWORDS

lactate, lactate clearance rate, delirium, MIMIC-IV, early stage of ICU

Introduction

Delirium is an acute psychiatric syndrome with the characteristics of a disturbance in attention and cognition (1). In the intensive care unit (ICU), delirium is a common complication, and its prevalence rates amount to approximately 22.0%, which has a strong influence on patients' treatment during the ICU stay as well as the prognosis after discharge (2, 3). As the pathogenesis of delirium is still unclear, it is of great significance to explore the biological indexes for delirium identification in the early stage that could improve delirium prognosis and reduce disease burden.

It has been speculated that delirium may be related to the rupture of the blood–brain barrier (BBB) and that dynamically increased permeability is associated with neuroinflammation and lactate response (4). The serum lactate level on the ICU admission is commonly used as a biomarker to assess disease severity and predict outcomes in patients, such as sepsis, septic shock, general trauma, or traumatic brain injury (TBI) (5, 6). The elevated serum lactate levels are most likely correlated with a persistent oxygen delivery deficit or a damaged microcirculation resulting in tissue ischemia (7). In addition, lactate is an important metabolism substrate, and the abnormal change in its concentration can indicate an imbalance of cerebral metabolism, which can be used to predict neurological function impairment and outcomes (8). Research studies have reported that serum lactate metabolism was linked to several central nervous system (CNS) diseases (e.g., mild cognitive impairment and cognitive recovery after TBI) (9–11). A previous retrospective cohort study suggested that serum lactate level 1 h after surgery may be a predictor of postoperative delirium (POD) development in elderly trauma patients (12).

In recent years, the lactate clearance rate has been proposed to be a better biomarker for prognosis in critical patients compared to the time point lactate level. The lactate clearance rate is closely associated with capillary perfusion independent of hemodynamic variables, which can reflect treatment efficacy and disease progression over a period of time (13, 14). A retrospective study in patients with acute gastrointestinal (GI) bleeding validated that lactate clearance rate at 3-h intervals was useful for early prediction of mortality and other prognoses (15). A latest study based on the Medical Information Mart for Intensive Care (MIMIC) database showed high lactate clearance rate between 0 and 12 h of mechanical ventilation was associated with a decreased risk of 30-day mortality in ICU patients (7). Nevertheless, the associations of lactate clearance rate with delirium risk are unclear.

Herein, this study aimed to investigate the associations of lactate and lactate clearance rate with delirium in ICU patients and assess the associations of lactate and lactate clearance rate with short-term mortality in delirium patients, to provide some references for further exploration on early biomarkers of delirium and prognosis improvement.

Methods

Study design and population

This was a retrospective cohort study. Data of participants were extracted from the MIMIC-IV database. The MIMIC-IV is intended to support a wide variety of research in healthcare because it contains true hospitalized patients admitted to a tertiary academic medical center in Boston, MA, United States, in 2012–2019. Comprehensive data on laboratory measurements, medications administered, and vital signs of each patient when they stayed in the hospital were documented and included in the MIMIC-IV (16).

First, we included 53,569 patients hospitalized in the ICU for the first time from the database. The inclusion criteria were as follows: (1) aged ≥18 years old, (2) stayed in the ICU >1 day, (3) having information on serum lactate concentration examined between 0 and 24 h of the ICU admission (T0) and that after 24 h of the ICU admission (T1), and (4) not diagnosed with coma or delirium within 24-h stay. Patients were excluded if they had one of the following situations: dementia, psychoses, TBI, dyslexia, intellectual disability, nervous system diseases, or alcohol/drug abuse. Finally, 7,812 patients were eligible. The MIMIC-IV has been approved by Institutional Review Boards (IRBs) of the Massachusetts Institute of Technology (MIT) and the Beth Israel Deaconess Medical Center (BIDMC) (17). As this database is publicly available, the IRB of the hospital waived the ethical approval.

Measurements of serum lactate and lactate clearance rate

We extracted information on serum lactate concentration (taken from arterial blood gases) at two time points, including the first examination between 0 and 24 h of the ICU admission (T0 lactate) and the first examination after 24 h of admission (T1 lactate). Then, the serum lactate levels were divided into three categories according to previous studies (18, 19): normal lactate level (<2 mmol/L), hyperlactatemia (2–5 mmol/L and PH > 7.35), and lactic acidosis (>5 mmol/L and PH < 7.35). In addition, the lactate clearance rate was calculated through the formula: lactate clearance rate = (T0 lactate − T1 lactate)/T0 lactate × 100%, and it was categorized into <0, 0–50, and > 50% levels (20).

Diagnosis of delirium

Two steps were conducted to identify delirium. First, the Richmond Agitation and Sedation Scale (RASS) was used to assess delirium. An individual with an RASS score < −3 was recognized as being in a coma and did not conform to the standard of the next step assessment (21). Then, delirium in eligible persons (with RASS score ≥ −3) was assessed using the Confusion Assessment Method for

the ICU (CAM-ICU). The CAM-ICU consists of four features, including feature 1: acute change or fluctuating course of mental status; feature 2: inattention; feature 3: disorganized thinking; and feature 4: altered level of consciousness (LOC) (22). When features 1 and 2 are present with either feature 3 or 4, patients were considered CAM-ICU positive and have a delirious status (23).

Outcomes and follow-up period

The study outcomes were as follows: (1) occurrence of delirium after 24 h of the ICU admission in the total population and (2) 30-day mortality in patients with delirium. The site of both delirium and mortality events included during ICU stay or after discharge. In-hospital information was recorded by the hospital department, and out-of-hospital information was recorded by the Social Security Bureau. Hence, the information on 30-day mortality in the MIMIC-IV was extracted from the patients' self-case. The follow-up started from the first time of ICU admission and ended when patients were discharged or died or 30 days after the ICU admission. Patients with outcome events after 30 days were not censored.

Variable extraction

We also extracted the following variables from the MIMIC-IV database: age, gender, insurance, heart rate (HR), diastolic blood pressure (DBP), systolic blood pressure (SBP), respiratory rate (RR), temperature, SPO_2, pH, white blood cell (WBC), red cell distribution width (RDW), platelet, hematocrit, creatinine (Cr), international normalized ratio (INR), prothrombin time (PT), blood urea nitrogen (BUN), bicarbonate, sodium (Na), potassium (K), chloride, glucose, the Sequential Organ Failure Assessment (SOFA), the Charlson Comorbidity Index (CCI), the Glasgow Coma Scale (GCS), sepsis, cardiovascular disease (CVD), diabetes mellitus (DM), hypertension, chronic kidney disease (CKD), liver disease, depression, ventilator-associated pneumonia (VAP), ventilation, use of vasopressors, sedative drug use, and antibiotic drug use. Additionally, information on these variables was measured and recorded for the first time within 24 h of the ICU admission.

Statistical analysis

The continuous variables are presented as median and quartiles [M (Q1, Q3)]. The Wilcoxon rank-sum test was used to compare the difference between the delirium and non-delirium groups. Frequency and composition ratio [*N* (%)] was used to describe classified variables, and the chi-square test (χ^2) was used for comparison between the delirium and non-delirium groups.

A univariable logistic regression analysis was used to screen covariates, and variables significantly associated with delirium were recognized as potential covariates and included in the adjustment of multivariate models. An exploration of the associations of serum lactate and lactate clearance rate with delirium was made through univariable and multivariable logistic regression analyses. The evaluation indexes were odds ratios (ORs) and 95% confidence intervals (CIs). The multicollinearity among study variables in logistic regression models was assessed through the variance inflation factor (VIF) method (Supplementary Table S1). The average VIF value less than 5 indicates no multicollinearity.

The relationships of lactate and lactate clearance rate with 30-day mortality in patients with delirium were found using univariable and multivariable Cox regression analyses. Similarly, univariable Cox regression analysis was used for the screening of covariates. The Cox model is a classical technique for performing analyses on time-to-event data (24). The evaluation indexes were hazard ratios (HRs) and 95% CIs, namely, the estimated risk of a given endpoint associated with a specific risk factor. The Cox proportional hazard model fit statistics were assessed by the Schoenfeld individual test (Supplementary Figure S1).

The Kaplan–Meier (KM) curves were drawn to evaluate mortality distributions among patients with different serum lactate levels. Among the multivariate models, model 1 adjusted for demographic and vital signs variables (including race, HR, DBP, SBP, RR, SPO_2, and pH); model 2 adjusted for demographic, vital signs, and laboratory examination variables (including race, HR, DBP, SBP, RR, SPO_2, pH, RDW, platelet, Cr, INR, PT, BUN, bicarbonate, and Na); model 3 adjusted for all selected covariates (including race, HR, DBP, SBP, RR, SPO_2, pH, RDW, platelet, Cr, INR, PT, BUN, bicarbonate, Na, SOFA, CCI, GCS, sepsis, CVD, liver disease, ventilation, use of vasopressors, VAP, sedative drug use, and antibiotic drug use). In addition, subgroup analyses of age, gender, sepsis, hypertension, sedative drug use, ventilation, antibiotic drug use, use of vasopressors, and the SOFA score were performed. Two-sided $p < 0.05$ indicates a significant difference. Statistics analyses were completed using SAS 9.4 (SAS Institute., Cary, NC, United States) and R version 4.2.3 (2023-04-17 ucrt).

Results

Characteristics of eligible participants

The flowchart of the study process is shown in Figure 1. A total of 53,569 individuals were admitted to the ICU for the first time in the MIMIC-IV database. Patients aged <18 years old ($n = 95$), stayed in the ICU ≤1 day ($n = 11,265$), without information on T0 or T1 lactate ($n = 32,625$), diagnosed with coma or delirium within 24 h of the ICU stay ($n = 409$), diagnosed with dementia ($n = 320$), psychoses ($n = 121$), TBI ($n = 376$), dyslexia ($n = 3$), intellectual disability ($n = 12$), nervous system diseases ($n = 297$), or alcohol/drug abuse ($n = 234$) were excluded. Finally, 7,812 patients were eligible.

Table 1 shows the characteristics of patients between the delirium and the non-delirium groups. The median age of the total study population was 65 years old, and 3,327 (42.59%) were women. Between the non-delirium and delirium groups, the median values of T0 lactate (2.00 mmol/L vs. 2.10 mmol/L), T1 lactate (1.40 mmol/L vs. 1.50 mmol/L), and lactate clearance rate (26.92% vs. 22.22%) were, respectively, different. In addition, race, HR, DBP, SBP, RR, SPO_2, pH, RDW, platelet, Cr, INR, PT, BUN, bicarbonate, Na, SOFA, CCI, GCS, sepsis, CVD, liver disease, ventilation, use of vasopressors, VAP, sedative drug use, and antibiotic drug use were significantly different between these two groups ($p < 0.05$).

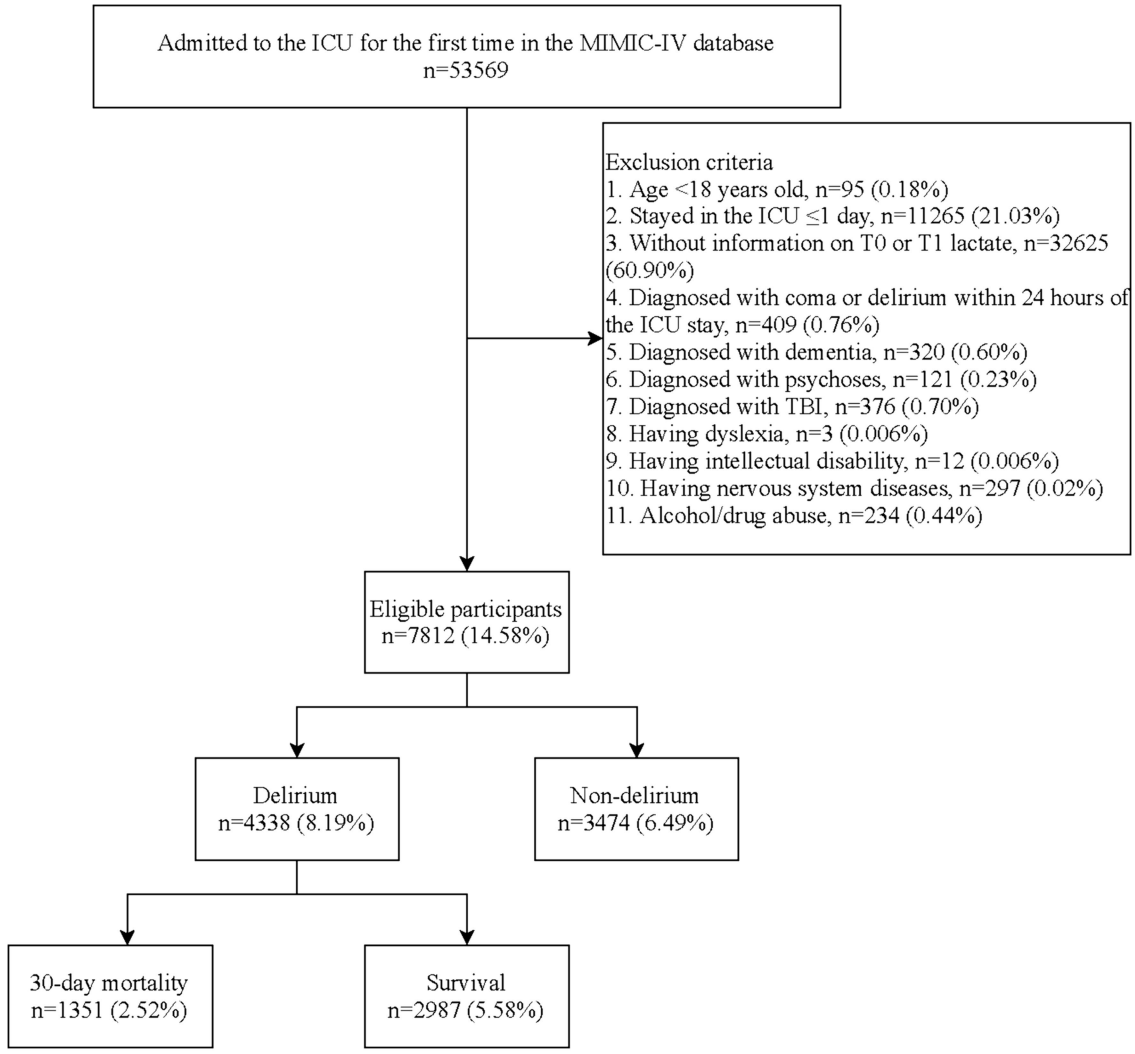

FIGURE 1
Flowchart of the study participants screening.

Associations of lactate and lactate clearance rate with delirium

We explored the associations of serum lactate levels and lactate clearance rate with delirium (Table 2). After adjusting for all covariates, the odds of delirium increased by 1.062 with T1 lactate elevated by 1 mmol/L (95%CI: 1.001–1.126), whereas the odds of delirium decreased by 0.081 with lactate clearance rate elevated by 1% (95%CI: 0.873–0.967). Patients with lactic acidosis at T0 seemed to have higher odds of delirium compared to those who had normal lactate levels (OR = 1.235, 95%CI: 1.105–1.382). Hyperlactatemia at T1 was also positively associated with delirium odds compared to normal lactate levels (OR = 1.277, 95%CI: 1.126–1.447). Lactate clearance rate > 50 may be a potential protective factor for delirium in ICU patients (OR = 0.705, 95%CI: 0.613–0.811). In addition, it was clearly shown in Figure 2 that patients with lactic acidosis (both at T0 and T1) had the lowest survival probability, followed by those with hyperlactatemia (all $p < 0.05$).

Furthermore, the association of lactate clearance rate with delirium in patients who had different T0 lactate levels was assessed. Supplementary Figure S2 shows that among patients with hyperlactatemia/lactic acidosis at T0, the proportion of delirium individuals gradually decreased along with the increased lactate clearance rate. Similarly, after adjusting for covariates, elevated lactate clearance rate was significantly associated with decreased odds of delirium in patients with hyperlactatemia/lactic acidosis at T0 (OR = 0.901, 95%CI: 0.835–0.973). Compared to lactate clearance rate < 0, lactate clearance rates of 0–50% (OR = 0.792, 95%CI: 0.643–0.976) and > 50% (OR = 0.620, 95%CI: 0.500–0.768) were both linked to lower odds of delirium in patients with hyperlactatemia/lactic acidosis at T0.

Associations of lactate and lactate clearance rate with delirium in subgroups

The relationships between lactate/lactate clearance rate and delirium were also explored in subgroups of age, gender, sepsis,

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TABLE 1 Characteristics of eligible participants.

Variables	Total (n = 7,812)	Non-delirium (n = 3,474)	Delirium (n = 4,338)	Statistic	p
Age, years, M (Q_1, Q_3)	65.00 (54.00, 76.00)	65.00 (54.00, 75.00)	65.00 (54.00, 76.00)	$Z = -0.196$	0.845
Gender, n (%)				$\chi^2 = 0.578$	0.447
Female	3,327 (42.59)	1,463 (42.11)	1,864 (42.97)		
Male	4,485 (57.41)	2,011 (57.89)	2,474 (57.03)		
Race, n (%)				$\chi^2 = 27.178$	<0.001
White	5,022 (64.29)	2,343 (67.44)	2,679 (61.76)		
Other	2,790 (35.71)	1,131 (32.56)	1,659 (38.24)		
Insurance, n (%)				$\chi^2 = 3.896$	0.143
Medicaid	550 (7.04)	223 (6.42)	327 (7.54)		
Medicare	3,486 (44.62)	1,551 (44.65)	1,935 (44.61)		
Other	3,776 (48.34)	1,700 (48.93)	2,076 (47.86)		
HR, bpm, M (Q_1, Q_3)	90.00 (78.00, 107.00)	89.00 (78.00, 104.00)	92.00 (79.00, 108.00)	$Z = -4.143$	<0.001
DBP, mmHg, M (Q_1, Q_3)	64.00 (54.00, 76.00)	63.50 (54.00, 75.00)	65.00 (54.00, 78.00)	$Z = -3.202$	0.001
SBP, mmHg, M (Q_1, Q_3)	117.00 (102.00, 135.00)	116.00 (101.00, 133.00)	118.00 (103.00, 136.00)	$Z = -3.203$	0.001
RR, insp/min, M (Q_1, Q_3)	19.00 (16.00, 24.00)	18.00 (15.00, 23.00)	20.00 (16.00, 24.00)	$Z = -7.589$	<0.001
Temperature, °C, M (Q_1, Q_3)	36.70 (36.33, 37.11)	36.67 (36.33, 37.06)	36.72 (36.39, 37.17)	$Z = -4.422$	<0.001
SPO_2, %, M (Q_1, Q_3)	98.00 (95.00, 100.00)	98.00 (95.00, 100.00)	98.00 (95.00, 100.00)	$Z = -3.126$	0.002
pH, M (Q_1, Q_3)	7.36 (7.28, 7.42)	7.37 (7.30, 7.42)	7.34 (7.26, 7.41)	$Z = -10.707$	<0.001
WBC, K/UL, M (Q_1, Q_3)	12.40 (8.60, 17.60)	12.10 (8.50, 17.20)	12.70 (8.70, 17.90)	$Z = -2.938$	0.003
RDW, %, M (Q_1, Q_3)	14.70 (13.60, 16.40)	14.55 (13.50, 16.00)	14.80 (13.70, 16.60)	$Z = -6.908$	<0.001
Platelet, K/UL, M (Q_1, Q_3)	175.00 (121.00, 247.00)	178.00 (126.00, 252.00)	173.00 (116.00, 243.00)	$Z = -3.334$	<0.001
Hematocrit, %, M (Q_1, Q_3)	32.00 (27.00, 37.10)	32.00 (27.10, 36.90)	32.00 (27.00, 37.27)	$Z = -0.367$	0.714
Cr, mg/dL, M (Q_1, Q_3)	1.10 (0.80, 1.80)	1.00 (0.80, 1.60)	1.20 (0.80, 1.90)	$Z = -8.798$	<0.001
INR, M (Q_1, Q_3)	1.40 (1.20, 1.70)	1.30 (1.20, 1.60)	1.40 (1.20, 1.70)	$Z = -2.566$	0.010
PT, s, M (Q_1, Q_3)	14.90 (13.00, 18.30)	14.80 (13.00, 17.80)	15.00 (13.00, 18.70)	$Z = -1.871$	0.061
BUN, mg/dL, M (Q_1, Q_3)	22.00 (15.00, 37.00)	21.00 (14.00, 33.00)	24.00 (16.00, 40.75)	$Z = -8.813$	<0.001
Bicarbonate, mEq/L, M (Q_1, Q_3)	21.00 (18.00, 24.00)	22.00 (19.00, 24.00)	21.00 (18.00, 24.00)	$Z = -6.842$	<0.001
Na, mEq/L, M (Q_1, Q_3)	138.00 (134.00, 141.00)	137.00 (134.00, 140.00)	138.00 (135.00, 141.00)	$Z = -7.087$	<0.001
K, mEq/L, M (Q_1, Q_3)	4.20 (3.80, 4.80)	4.30 (3.80, 4.80)	4.20 (3.70, 4.80)	$Z = -1.799$	0.072
Chloride, mEq/L, M (Q_1, Q_3)	104.00 (100.00, 108.00)	104.00 (100.00, 108.00)	104.00 (100.00, 108.00)	$Z = -0.607$	0.544
Glucose, mg/dL, M (Q_1, Q_3)	140.00 (112.00, 183.00)	138.00 (111.00, 179.00)	141.00 (112.00, 185.00)	$Z = -1.881$	0.060
SOFA, M (Q_1, Q_3)	3.00 (1.00, 5.00)	3.00 (1.00, 5.00)	3.00 (1.00, 6.00)	$Z = -10.285$	<0.001
CCI, M (Q_1, Q_3)	3.00 (1.00, 5.00)	3.00 (1.00, 4.00)	3.00 (1.00, 5.00)	$Z = -6.035$	<0.001
GCS, M (Q_1, Q_3)	15.00 (15.00, 15.00)	15.00 (15.00, 15.00)	15.00 (15.00, 15.00)	$Z = -5.700$	<0.001
Sepsis, n (%)				$\chi^2 = 185.333$	<0.001
No	4,517 (57.82)	2,304 (66.32)	2,213 (51.01)		
Yes	3,295 (42.18)	1,170 (33.68)	2,125 (48.99)		
CVD, n (%)				$\chi^2 = 9.112$	0.003
No	3,223 (41.26)	1,368 (39.38)	1,855 (42.76)		
Yes	4,589 (58.74)	2,106 (60.62)	2,483 (57.24)		
DM, n (%)				$\chi^2 = 1.413$	0.235
No	5,348 (68.46)	2,354 (67.76)	2,994 (69.02)		
Yes	2,464 (31.54)	1,120 (32.24)	1,344 (30.98)		
Hypertension, n (%)				$\chi^2 = 2.218$	0.136

(Continued)

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TABLE 1 (Continued)

Variables	Total (*n* = 7,812)	Non-delirium (*n* = 3,474)	Delirium (*n* = 4,338)	Statistic	*p*
No	4,720 (60.42)	2,067 (59.50)	2,653 (61.16)		
Yes	3,092 (39.58)	1,407 (40.50)	1,685 (38.84)		
CKD, *n* (%)				$\chi^2 = 1.496$	0.221
No	6,355 (81.35)	2,847 (81.95)	3,508 (80.87)		
Yes	1,457 (18.65)	627 (18.05)	830 (19.13)		
Liver disease, n (%)				$\chi^2 = 38.862$	<0.001
No	6,267 (80.22)	2,896 (83.36)	3,371 (77.71)		
Yes	1,545 (19.78)	578 (16.64)	967 (22.29)		
Depression, *n* (%)				$\chi^2 = 6.228$	0.013
No	7,227 (92.51)	3,185 (91.68)	4,042 (93.18)		
Yes	585 (7.49)	289 (8.32)	296 (6.82)		
Ventilation, *n* (%)				$\chi^2 = 483.178$	<0.001
Mechanical ventilation	4,850 (62.08)	1,716 (49.40)	3,134 (72.25)		
Supplemental oxygen	2,644 (33.85)	1,507 (43.38)	1,137 (26.21)		
None	318 (4.07)	251 (7.23)	67 (1.54)		
Vasopressors, *n* (%)				$\chi^2 = 241.645$	<0.001
No	2,300 (29.44)	1,334 (38.40)	966 (22.27)		
Yes	5,512 (70.56)	2,140 (61.60)	3,372 (77.73)		
VAP, *n* (%)				$\chi^2 = 329.321$	<0.001
No	7,148 (91.5)	3,401 (97.90)	3,747 (86.38)		
Yes	664 (8.5)	73 (2.10)	591 (13.62)		
Sedative drug, *n* (%)				$\chi^2 = 729.083$	<0.001
No	1,625 (20.8)	1,204 (34.66)	421 (9.70)		
Yes	6,187 (79.2)	2,270 (65.34)	3,917 (90.30)		
Antibiotic drug, *n* (%)				$\chi^2 = 325.903$	<0.001
No	798 (10.22)	595 (17.13)	203 (4.68)		
Yes	7,014 (89.78)	2,879 (82.87)	4,135 (95.32)		
T0 lactate, mmol/L, M (Q_1, Q_3)	2.10 (1.40, 3.30)	2.00 (1.30, 3.10)	2.10 (1.40, 3.50)	$Z = -3.240$	0.001
T1 lactate, mmol/L, M (Q_1, Q_3)	1.50 (1.10, 2.20)	1.40 (1.10, 2.00)	1.50 (1.10, 2.40)	$Z = -7.877$	<0.001
Lactate clearance rate, %, M (Q_1, Q_3)	25.00 (−8.33, 50.00)	26.92 (−6.25, 51.27)	22.22 (−9.15, 48.00)	$Z = -3.878$	<0.001
T0 lactate, *n* (%)				$\chi^2 = 41.876$	<0.001
Normal lactate level	3,649 (46.71)	1,627 (46.83)	2,022 (46.61)		
Hyperlactatemia	3,236 (41.42)	1,522 (43.81)	1,714 (39.51)		
Lactic acidosis	927 (11.87)	325 (9.36)	602 (13.88)		
T1 lactate, *n* (%)				$\chi^2 = 67.316$	<0.001
Normal lactate level	5,434 (69.56)	2,577 (74.18)	2,857 (65.86)		
Hyperlactatemia	1,898 (24.3)	736 (21.19)	1,162 (26.79)		
Lactic acidosis	480 (6.14)	161 (4.63)	319 (7.35)		
Lactate clearance rate, %, *n* (%)				$\chi^2 = 10.683$	0.005
<0	2,522 (32.28)	1,069 (30.77)	1,453 (33.49)		
0–50	3,449 (44.15)	1,533 (44.13)	1,916 (44.17)		
>50	1,841 (23.57)	872 (25.10)	969 (22.34)		
30-day mortality, *n* (%)				$\chi^2 = 243.608$	<0.001

(Continued)

TABLE 1 (Continued)

Variables	Total (n = 7,812)	Non-delirium (n = 3,474)	Delirium (n = 4,338)	Statistic	p
No	5,909 (75.64)	2,922 (84.11)	2,987 (68.86)		
Yes	1,903 (24.36)	552 (15.89)	1,351 (31.14)		

Z: The Wilcoxon rank-sum test, χ^2: chi-square test. M, Median; Q_1, First quartile; Q_3, Third quartile; HR, Heart rate; DBP, Diastolic blood pressure; SBP, Systolic blood pressure; RR, Respiratory rate; WBC, White blood cell; RDW, Red cell distribution width; Cr, Creatinine; INR, International normalized ratio; PT, Prothrombin time; BUN, Blood urea nitrogen; Na, Sodium; K, Potassium; SOFA, The Sequential organ failure assessment; CCI, The Charlson comorbidity index; GCS, The Glasgow Coma Scale; CVD, Cardiovascular disease; DM, Diabetes mellitus; CKD, Chronic kidney disease; VAP, Ventilator-associated pneumonia; T0, Serum lactate concentration examined at the ICU admission; T1, The first examination of serum lactate concentration within 24 h of the ICU admission.

TABLE 2 Associations of lactate and lactate clearance rate with delirium.

Exposure	Model 1		Model 2		Model 3	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
T0 lactate	1.070 (1.015–1.127)	0.011	1.047 (0.989–1.108)	0.112	0.965 (0.907–1.027)	0.266
T1 lactate	1.138 (1.079–1.200)	<0.001	1.102 (1.044–1.164)	<0.001	1.062 (1.001–1.126)	0.045
Lactate clearance rate	0.913 (0.870–0.958)	<0.001	0.916 (0.872–0.962)	<0.001	0.919 (0.873–0.967)	0.001
T0 lactate						
Normal lactate level	Ref		Ref		Ref	
Hyperlactatemia	1.645 (1.414–1.914)	<0.001	1.220 (1.039–1.432)	0.015	1.088 (0.909–1.302)	0.359
Lactic acidosis	1.104 (1.004–1.214)	0.042	1.161 (1.053–1.280)	0.003	1.235 (1.105–1.382)	<0.001
T1 lactate						
Normal lactate level	Ref		Ref		Ref	
Hyperlactatemia	1.424 (1.280–1.584)	<0.001	1.370 (1.229–1.528)	<0.001	1.277 (1.126–1.447)	<0.001
Lactic acidosis	1.787 (1.468–2.176)	<0.001	1.364 (1.114–1.671)	0.003	1.079 (0.859–1.354)	0.514
Lactate clearance rate						
<0	Ref		Ref		Ref	
0–50	0.920 (0.829–1.020)	0.113	0.883 (0.795–0.981)	0.021	0.926 (0.824–1.042)	0.203
>50	0.818 (0.724–0.923)	0.001	0.729 (0.644–0.826)	<0.001	0.705 (0.613–0.811)	<0.001

OR, Odds ratio; CI, Confidence interval; T0, Serum lactate concentration examined at the ICU admission; T1, The first examination of serum lactate concentration within 24 h of the ICU admission; Ref, Reference. Mode1 1: adjusted for race, HR, DBP, SBP, RR, SPO_2, and pH; Model 2: adjusted for race, HR, DBP, SBP, RR, SPO_2, pH, RDW, platelet, Cr, INR, PT, BUN, bicarbonate, and Na; Model 3: adjusted for race, HR, DBP, SBP, RR, SPO_2, pH, RDW, platelet, Cr, INR, PT, BUN, bicarbonate, Na, SOFA, CCI, GCS, sepsis, CVD, liver disease, ventilation, use of vasopressors, VAP, sedative drug use, and antibiotic drug use.

hypertension, sedative drugs, ventilation, antibiotic drugs, vasopressors, and SOFA score (divided according to the median values) (Figure 3). T1 lactate had a positive association with delirium in patients without hypertension (OR = 1.080, 95%CI: 1.000–1.166), not use sedative drug (OR = 1.128 95%CI: 1.002–1.269), or with SOFA score ≤ 3 (OR = 1.090, 95%CI: 1.003–1.184). In addition, a higher lactate clearance rate was associated with lower odds of delirium in people aged ≥65 years old, female, male, non-sepsis, sepsis, non-hypertension, non-sedative drug use, sedative drug use, ventilation, antibiotic drug use, use of vasopressors, SOFA score > 3, and SOFA score ≤ 3 subgroups (all $p < 0.05$).

Associations of lactate and lactate clearance rate with 30-day mortality in delirium patients

We further investigated the associations of lactate and lactate clearance rate with 30-day mortality in patients with delirium (Table 3). After adjusting for all covariates, T0 lactate (OR = 1.152, 95%CI: 1.096–1.211) and T1 lactate (OR = 1.423, 95%CI: 1.370–1.479) were both positively associated with 30-day mortality, whereas a higher lactate clearance rate was linked to a lower risk of 30-day mortality in delirium patients (OR = 0.855, 95%CI: 0.826–0.886). Compared to normal lactate levels, hyperlactatemia and lactic acidosis (whether at T0 or T1) were potential risk factors for 30-day mortality in delirium, while lactate clearance rate ≥ 0 had a potential protective value for 30-day mortality (all $p < 0.05$).

Discussion

The current research investigated the associations of lactate and lactate clearance rate with delirium among ICU patients and the associations of lactate and lactate clearance rate with 30-day mortality in delirium patients. The results showed that compared to patients with normal lactate levels, those who had lactic acidosis at T0 or hyperlactatemia at T1 seemed to have higher odds of delirium. On the contrary, a lactate clearance rate > 50 was associated with lower odds of delirium. In addition, elevated T0 lactate and T1 lactate were both potential risk factors for 30-day

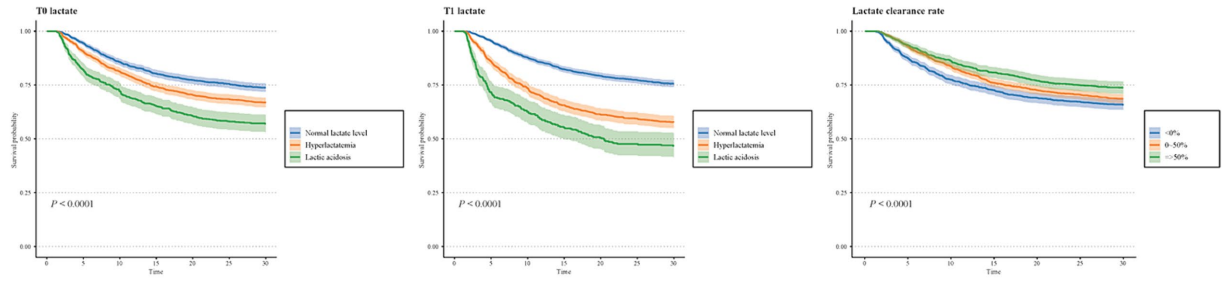

FIGURE 2
Associations of T0 lactate, T1 lactate, and lactate clearance rate with delirium in subgroups of age, gender, sepsis, hypertension, sedative drug, ventilation, antibiotic drug, vasopressors, and SOFA score.

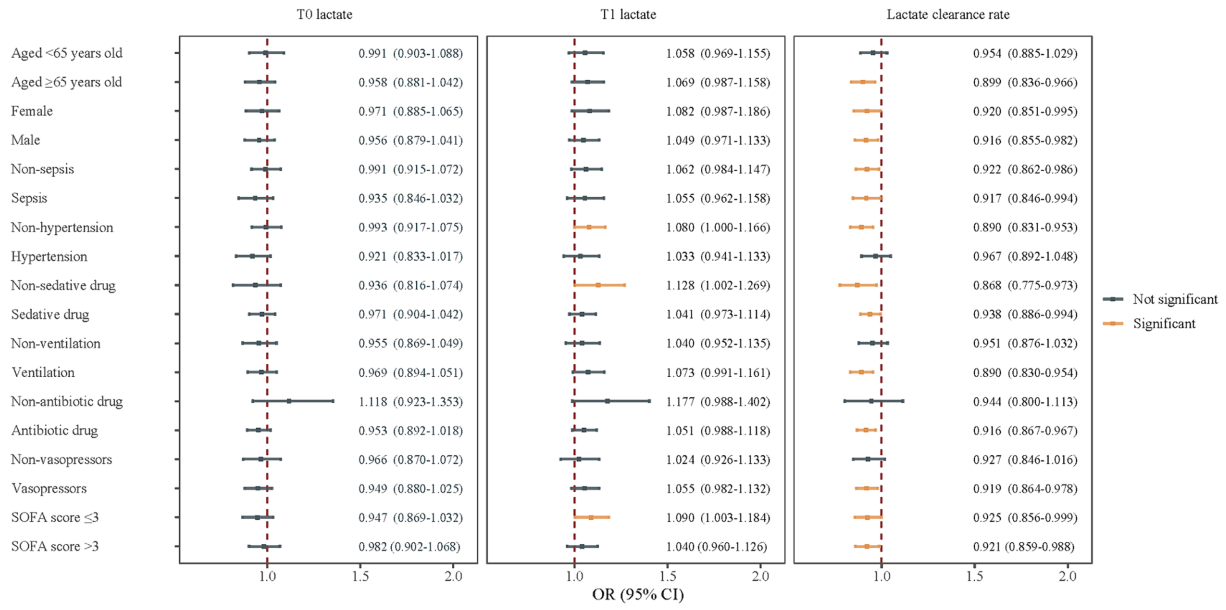

FIGURE 3
Associations of lactate and lactate clearance rate with delirium in subgroups of age, gender, sepsis, hypertension, sedative drug, ventilation, antibiotic drug, vasopressors, and SOFA score.

mortality in patients with delirium, whereas a higher lactate clearance rate was linked to a lower risk of 30-day mortality.

To the best of our knowledge, it was the first time to investigate the association of serum lactate at different time points and lactate clearance rate with the occurrence of delirium in the general patients who stayed in the ICU. A previous retrospective cohort study on elderly trauma patients from a level 1 single trauma center showed that serum lactate levels on ICU admission and 1 h after surgery were predictors of postoperative delirium (12). Wang et al. (25) performed a prospective observational study and identified postoperative lactate levels as an independent predictor of delirium in patients who underwent cardiac surgery at the Nanjing Drum Tower Hospital, China. In the present study, we found serum lactate level after 24 h of ICU admission (T1 lactate level) was a potential risk factor for delirium. Compared to previous research studies, our findings relatively supplemented the association of serum lactate level with delirium among the ICU general population. In addition, the study participants were extracted from the MIMIC-IV database, which contains a large sample of true hospitalized patients in the United States. Unfortunately, according to our results, the odds of delirium were not significantly increased along with the elevated T0 lactate levels, indicating there may be no linear relationship between them. Similarly, Liu et al. (8) demonstrated that the serum lactate at ICU admission was not correlated with neurological function impairment in adult patients under general anesthesia elective neurosurgery after the surgery at The Seventh Medical Center of the General Hospital of the People's Liberation Army of China. In the current research, 46.71% of participants had normal lactate levels at T0 (<2 mmol/L) and 41.42% had hyperlactatemia (2–5 mmol/L and pH > 7.35), whereas patients after the surgery in the study by Liu had higher serum lactate than normal commonly (3.4–4.1 mmol/L) (8). In fact, fluid transfusion and vasoactive agent use might affect serum lactate levels during the ICU stay; thus, we adjusted for sedative drug use and antibiotic drug use in multivariate models and found that compared to patients with normal T0 lactate levels, those who had hyperlactatemia seemed to have higher odds of delirium after 24 h of

TABLE 3 Associations of lactate and lactate clearance rate with 30-day mortality in patients with delirium.

Variables	Model 1		Model 2		Model 3	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
T0 lactate	1.157 (1.107–1.210)	<0.001	1.152 (1.096–1.211)	<0.001	1.132 (1.074–1.193)	<0.001
T1 lactate	1.433 (1.383–1.485)	<0.001	1.423 (1.370–1.479)	<0.001	1.409 (1.355–1.465)	<0.001
Lactate clearance rate	0.863 (0.834–0.892)	<0.001	0.855 (0.826–0.886)	<0.001	0.861 (0.831–0.891)	<0.001
T0 lactate						
Normal lactate level	Ref		Ref		Ref	
Hyperlactatemia	1.265 (1.123–1.425)	<0.001	1.251 (1.106–1.416)	<0.001	1.194 (1.054–1.353)	0.005
Lactic acidosis	1.586 (1.343–1.872)	<0.001	1.568 (1.315–1.869)	<0.001	1.448 (1.211–1.731)	<0.001
T1 lactate						
Normal lactate level	Ref		Ref		Ref	
Hyperlactatemia	1.898 (1.688–2.134)	<0.001	1.726 (1.529–1.949)	<0.001	1.657 (1.466–1.873)	<0.001
Lactic acidosis	2.615 (2.195–3.114)	<0.001	2.446 (2.042–2.929)	<0.001	2.275 (1.895–2.730)	<0.001
Lactate clearance rate						
<0	Ref		Ref		Ref	
0–50	0.869 (0.772–0.977)	0.019	0.883 (0.784–0.994)	0.040	0.861 (0.764–0.970)	0.014
>50	0.624 (0.534–0.728)	<0.001	0.665 (0.567–0.781)	<0.001	0.638 (0.543–0.750)	<0.001

HR: hazard ratio, CI: confidence interval, T0: serum lactate concentration examined at the ICU admission, T1: the first examination of serum lactate concentration within 24 h of the ICU admission, Ref: reference. Mode1 1: adjusted for race, HR, DBP, SBP, RR, SPO_2, and pH; Model 2: adjusted for race, HR, DBP, SBP, RR, SPO_2, pH, RDW, platelet, Cr, INR, PT, BUN, bicarbonate, and Na; and Model 3: adjusted for race, HR, DBP, SBP, RR, SPO_2, pH, RDW, platelet, Cr, INR, PT, BUN, bicarbonate, Na, SOFA, CCI, GCS, sepsis, CVD, liver disease, ventilation, use of vasopressors, VAP, sedative drug use, and antibiotic drug use.

ICU admission. In addition, 69.56% of persons' serum lactate levels could return to normal levels within 24 h. The relationship between T1 lactate and delirium suggests that it is necessary to continuously pay attention to lactate levels in clinical practice so as to timely adjust treatment or take appropriate measures to reduce the risk of delirium in ICU patients. Nevertheless, the causal associations of T0 and T1 lactate with delirium need to be further verified.

The underlying pathophysiology mechanisms that the association of serum lactate with delirium may be complex and diverse, where immunoinflammatory reaction, metabolic insufficiency, and cognitive disintegration are common hypotheses. Systemic inflammation results in diffuse microcirculatory impairment, including leukocyte adhering to vessel lining, endothelial cell swelling, perivascular edema, and narrowing of capillary diameters and lowers functional capillary density, leading to a decrease in nutritive perfusion and longer diffusion distances for oxygen (26). Acetylcholine synthesis is especially sensitive to low oxygen tension, and its deficiency plays an important role in delirium pathophysiology (26). Although patients with trauma may have severely reduced circulation and tissue hypoxia, their blood pressure may be in the normal range because of peripheral vasoconstriction (27). Similarly, in our study, delirium patients had significantly higher DBP and SBP than those without delirium, but hypertension was not significantly different between these two groups. In addition, the elevated serum lactate was considered a reflection of the elevation of intracerebral lactate concentration (28). As important cerebral metabolism substrates, intracerebral lactate and glucose will change similar concentrations when the brain's energy consumption balance is disrupted (a state of hypo-glucose and hyper-lactate concentration), indicating an acute metabolism crisis (ACMC) (28). ACMC is recognized as the etiology of secondary brain injury, which can cause acute neurological function impairment, such as different degrees of impairment of attention, executive ability, cognitive ability, and emotional disorders (29). Our findings indicated that not only patients with trauma but also the general population in the ICU should be carefully continuously focused on the serum lactate level within and after 24 h of the ICU admission. Therefore, serum lactate as a rapidly and inexpensively measured parameter could have the potential to be an early indicator of delirium occurrence among ICU patients in clinical practice.

Lactate clearance rate has been proposed to be a more descriptive term for the global tissue states compared to single lactate concentration at one time point and could be optimal for predicting mortality in critical patients (30, 31). No study has reported the association of lactate clearance rate with delirium so far; however, its predictive value in mortality of other common diseases in the ICU has gained a lot of support (31, 32). The underlying mechanisms that lactate clearance rate had a negative association with both delirium and 30-day mortality in ICU patients may be multitudinous. Lactate clearance rate early in the hospital course may indicate the resolution of global tissue hypoxia and further reduce the mortality rate (33). In addition, early lactate clearance was significantly associated with a decreased level of pro-inflammatory biomarkers, suggesting that lactate clearance rate could be an indirect prognostic marker (34). Although there is no clear biological mechanism to support the association of lactate clearance rate with delirium, we speculated that a higher lactate clearance rate may reduce the risk of delirium by improving the relative pathways, such as inflammatory response and

cerebrovascular changes. According to the study results, we hold the opinion that dynamic monitoring of lactate clearance rate (which is best to be maintained above 50%) in ICU patients may be valuable for reducing the risk of both delirium and 30-day mortality, especially in those who had baseline hyperlactatemia/lactic acidosis.

Subgroup analyses showed that among patients without hypertension, who did not use sedative drugs, or with SOFA score ≤ 3, T1 lactate level had a positive association with delirium odds. On the other hand, the association of higher lactate clearance rate with lower odds of delirium was found in age ≥ 65 years old, non-hypertension, ventilation, antibiotic drug, vasopressors, male, female, sepsis, sedative drug, and SOFA score subgroups. It has been reported that preexisting or non-modifiable risk factors for delirium include aging >65 years old, male sex, alcohol abuse, brain trauma, dementia, hypertension, polypharmacy, and multiple medical comorbidities (35–37). In the present study, maintaining a higher lactate clearance rate (more than 50%) in patients with advanced age, without hypertension, who received medication, or equipment-assisted treatment could reduce the odds of delirium after excluding those who had alcohol abuse, brain trauma, or dementia. In conclusion, our findings were consistent with those of previous studies mentioned above, which indicated that both serum lactate level at different time points and lactate clearance rate in general ICU patients should be focused, and the population with milder disease conditions or undergoing relatively comprehensive treatment should not be ignored.

There are some strengths and limitations of this research. The current study is the first to investigate the associations of serum lactate at different time points and lactate clearance rate with delirium and subsequent mortality risk in the early stage of the ICU stay. Meanwhile, on the basis of the MIMIC-IV database with a large sample size, we considered multi-dimensional influencing factors for analyses, and the results were relatively reliable. However, as a single-center retrospective study, it is hard to conclude causal associations of lactate and lactate clearance rate with delirium, and interpretation of the results is also limited by selection bias. In addition, due to the limitation of the MIMIC-IV database, we could not discuss more details on the median- and long-term prognoses of patients with delirium other than 30-day mortality.

Conclusion

Higher lactate levels at different time points of the ICU admission were associated with higher odds of delirium, whereas keeping a higher lactate clearance rate may reduce the potential risk of delirium and subsequent short-term mortality in delirium patients. However, further prospective studies are still needed to clarify the causal associations of lactate and lactate clearance rate with delirium.

Data availability statement

Publicly available datasets were analyzed in this study. The datasets generated and/or analyzed during the current study are available in the MIMIC IV database, https://mimic.physionet.org/iv/.

Author contributions

XQ: Writing – original draft, Writing – review & editing. YS: Data curation, Writing – review & editing. YJ: Methodology, Supervision, Writing – review & editing. YX: Writing – review & editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Publisher's note

Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fneur.2024.1371827/full#supplementary-material

References

1. Keenan CR, Jain S. Delirium. *Med Clin North Am*. (2022) 106:459–69. doi: 10.1016/j.mcna.2021.12.003

2. Pazouki R, Hasselblatt P, Kugler C. Prevalence of delirium in gastroenterology/hepatology units: a cross-sectional study. *Z Gastroenterol*. (2023) 61:1357–64. doi: 10.1055/a-2124-1874

3. Yan E, Veitch M, Saripella A, Alhamdah Y, Butris N, Tang-Wai DF, et al. Association between postoperative delirium and adverse outcomes in older surgical patients: a systematic review and meta-analysis. *J Clin Anesth*. (2023) 90:111221. doi: 10.1016/j.jclinane.2023.111221

4. Taylor J, Parker M, Casey CP, Tanabe S, Kunkel D, Rivera C, et al. Postoperative delirium and changes in the blood-brain barrier, neuroinflammation, and cerebrospinal fluid lactate: a prospective cohort study. *Br J Anaesth*. (2022) 129:219–30. doi: 10.1016/j.bja.2022.01.005

5. Bender M, Stein M, Schoof B, Kolodziej MA, Uhl E, Scholler K. Troponin I as an early biomarker of cardiopulmonary parameters during the first 24 h of intensive care unit treatment in isolated traumatic brain injury patients. *Injury*. (2020) 51:1189–95. doi: 10.1016/j.injury.2020.01.002

6. El-Menyar A, Goyal A, Latifi R, Al-Thani H, Frishman W. Brain-heart interactions in traumatic brain injury. *Cardiol Rev*. (2017) 25:279–88. doi: 10.1097/CRD.0000000000000167

7. Sheng B, Li S, Wang H, Guo Z, Zhang Z. Association between serum lactate, lactate clearance rate, and 30-day mortality among patients undergoing mechanical ventilation: a retrospective cohort study of MIMIC-III database. *Medicine (Baltimore)*. (2024) 103:e35818. doi: 10.1097/MD.0000000000035818

8. Liu D, Yao Q, Song B, Sun Y, Ju H, Li G. Serum lactate monitoring may help to predict neurological function impairment caused by acute metabolism crisis. *Sci Rep*. (2023) 13:2820. doi: 10.1038/s41598-023-29506-y

9. Mannino C, Glenn TC, Hovda DA, Vespa PM, McArthur DL, Van Horn JD, et al. Acute glucose and lactate metabolism are associated with cognitive recovery following traumatic brain injury. *J Neurosci Res*. (2018) 96:696–701. doi: 10.1002/jnr.24097

10. Pan H, Huang X, Li F, Ren M, Zhang J, Xu M, et al. Association among plasma lactate, systemic inflammation, and mild cognitive impairment: a community-based study. *Neurol Sci*. (2019) 40:1667–73. doi: 10.1007/s10072-019-03900-9

11. Proia P, Di Liegro CM, Schiera G, Fricano A, Di Liegro I. Lactate as a metabolite and a regulator in the central nervous system. *Int J Mol Sci*. (2016) 17:1450. doi: 10.3390/ijms17091450

12. Lee C, Lee J, Cho H, Song J, Jung H, Ma X, et al. The Association of Perioperative Serum Lactate Levels with postoperative delirium in elderly trauma patients. *Biomed Res Int*. (2019) 2019:3963780–7. doi: 10.1155/2019/3963780

13. Shu W, Wan J, Chen J, He W, Zhu Y, Zeng H, et al. Initially elevated arterial lactate as an independent predictor of poor outcomes in severe acute pancreatitis. *BMC Gastroenterol*. (2020) 20:116. doi: 10.1186/s12876-020-01268-1

14. Zeng J, Wan J, He W, Zhu Y, Zeng H, Liu P, et al. Prognostic value of arterial lactate metabolic clearance rate in moderate and severe acute pancreatitis. *Dis Markers*. (2022) 2022:9233199. doi: 10.1155/2022/9233199

15. Kim K, Lee DH, Lee DH, Choi YH, Bae SJ. Early lactate clearance for predicting outcomes in patients with gastrointestinal bleeding. *Ir J Med Sci*. (2023) 192:1923–9. doi: 10.1007/s11845-022-03185-6

16. Jhou HJ, Chen PH, Yang LY, Chang SH, Lee CH. Plasma anion gap and risk of in-hospital mortality in patients with acute ischemic stroke: analysis from the MIMIC-IV database. *J Pers Med*. (2021) 11:1004. doi: 10.3390/jpm11101004

17. Johnson AE, Stone DJ, Celi LA, Pollard TJ. The MIMIC code repository: enabling reproducibility in critical care research. *J Am Med Inform Assoc*. (2018) 25:32–9. doi: 10.1093/jamia/ocx084

18. Connelly PJ, Lonergan M, Soto-Pedre E, Donnelly L, Zhou K, Pearson ER. Acute kidney injury, plasma lactate concentrations and lactic acidosis in metformin users: a GoDarts study. *Diabetes Obes Metab*. (2017) 19:1579–86. doi: 10.1111/dom.12978

19. Lu T, Tan L, Xu K, Liu J, Liu C, Zhang G, et al. Outcomes of hyperlactatemia on admission in critically ill patients with acute myocardial infarction: a retrospective study from MIMIC-IV. *Front Endocrinol*. (2022) 13:1015298. doi: 10.3389/fendo.2022.1015298

20. Gharipour A, Razavi R, Gharipour M, Modarres R, Nezafati P, Mirkheshti N. The incidence and outcome of severe hyperlactatemia in critically ill patients. *Intern Emerg Med*. (2021) 16:115–23. doi: 10.1007/s11739-020-02337-9

21. Deljou A, Soleimani J, Martin DP, Schroeder DR, Sprung J, Weingarten TN. Anesthetic management and deep sedation after emergence from general anesthesia: a retrospective cohort study. *Anesth Analg*. (2023) 136:1154–63. doi: 10.1213/ANE.0000000000006470

22. Ely EW, Inouye SK, Bernard GR, Gordon S, Francis J, May L, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA*. (2001) 286:2703–10. doi: 10.1001/jama.286.21.2703

23. Chen TJ, Chung YW, Chang HR, Chen PY, Wu CR, Hsieh SH, et al. Diagnostic accuracy of the CAM-ICU and ICDSC in detecting intensive care unit delirium: a bivariate meta-analysis. *Int J Nurs Stud*. (2021) 113:103782. doi: 10.1016/j.ijnurstu.2020.103782

24. Abd ElHafeez S, D'Arrigo G, Leonardis D, Fusaro M, Tripepi G, Roumeliotis S. Methods to analyze time-to-event data: the cox regression analysis. *Oxidative Med Cell Longev*. (2021) 2021:1–6. doi: 10.1155/2021/1302811

25. Wang YP, Shen BB, Zhu CC, Li L, Lu S, Wang DJ, et al. Unveiling the nexus of postoperative fever and delirium in cardiac surgery: identifying predictors for enhanced patient care. *Front Cardiovasc Med*. (2023) 10:1237055. doi: 10.3389/fcvm.2023.1237055

26. Hala M. Pathophysiology of postoperative delirium: systemic inflammation as a response to surgical trauma causes diffuse microcirculatory impairment. *Med Hypotheses*. (2007) 68:194–6. doi: 10.1016/j.mehy.2006.07.003

27. Salottolo KM, Mains CW, Offner PJ, Bourg PW, Bar-Or D. A retrospective analysis of geriatric trauma patients: venous lactate is a better predictor of mortality than traditional vital signs. *Scand J Trauma Resusc Emerg Med*. (2013) 21:7. doi: 10.1186/1757-7241-21-7

28. Jalloh I, Helmy A, Howe DJ, Shannon RJ, Grice P, Mason A, et al. A comparison of oxidative lactate metabolism in traumatically injured brain and control brain. *J Neurotrauma*. (2018) 35:2025–35. doi: 10.1089/neu.2017.5459

29. Wright MJ, McArthur DL, Alger JR, Van Horn J, Irimia A, Filippou M, et al. Early metabolic crisis-related brain atrophy and cognition in traumatic brain injury. *Brain Imag Behav*. (2013) 7:307–15. doi: 10.1007/s11682-013-9231-6

30. Merkle-Storms J, Djordjevic I, Weber C, Avgeridou S, Krasivskyi I, Gaisendrees C, et al. Impact of lactate clearance on early outcomes in pediatric ECMO patients. *Medicina*. (2021) 57:284. doi: 10.3390/medicina57030284

31. Zhang Z, Xu X. Lactate clearance is a useful biomarker for the prediction of all-cause mortality in critically ill patients: a systematic review and meta-analysis*. *Crit Care Med*. (2014) 42:2118–25. doi: 10.1097/CCM.0000000000000405

32. Marbach JA, Stone S, Schwartz B, Pahuja M, Thayer KL, Faugno AJ, et al. Lactate clearance is associated with improved survival in cardiogenic shock: a systematic review and Meta-analysis of prognostic factor studies. *J Card Fail*. (2021) 27:1082–9. doi: 10.1016/j.cardfail.2021.08.012

33. Nguyen HB, Rivers EP, Knoblich BP, Jacobsen G, Muzzin A, Ressler JA, et al. Early lactate clearance is associated with improved outcome in severe sepsis and septic shock. *Crit Care Med*. (2004) 32:1637–42. doi: 10.1097/01.ccm.0000132904.35713.a7

34. Nguyen HB, Loomba M, Yang JJ, Jacobsen G, Shah K, Otero RM, et al. Early lactate clearance is associated with biomarkers of inflammation, coagulation, apoptosis, organ dysfunction and mortality in severe sepsis and septic shock. *J Inflamm*. (2010) 7:6. doi: 10.1186/1476-9255-7-6

35. Oh ES, Sieber FE, Leoutsakos JM, Inouye SK, Lee HB. Sex differences in hip fracture surgery: preoperative risk factors for delirium and postoperative outcomes. *J Am Geriatr Soc*. (2016) 64:1616–21. doi: 10.1111/jgs.14243

36. Pandharipande P, Cotton BA, Shintani A, Thompson J, Pun BT, Morris JA, et al. Prevalence and risk factors for development of delirium in surgical and trauma intensive care unit patients. *J Trauma*. (2008) 65:34–41. doi: 10.1097/TA.0b013e31814b2c4d

37. Popeo DM. Delirium in older adults. *Mt Sinai J Med*. (2011) 78:571–82. doi: 10.1002/msj.20267

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Exacerbation of delirium and epileptic seizures in an older man with idiopathic Parkinson's disease due to multiple prescriptions: a case report

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Introduction: Parkinson's disease (PD) is a disorder characterized by motor symptoms, such as rigidity, akinesia, and resting tremor, as well as non-motor symptoms, including psychiatric manifestations and autonomic failure. The prevalence of PD increases with age, and the condition is more common in men than in women. Conversely, polypharmacy has emerged as a paramount medical concern, especially among older patients, correlating with medicines' adverse effects, interactions between medicines, frequent admissions to the hospital, and a high risk of morbidity and mortality.

Case description: We encountered an older male patient with idiopathic PD and mild renal dysfunction. Originally prescribed 14 types of medicines, including anti-PD drugs, the patient developed delirium and epileptic seizures during hospitalization. After reducing the number of medications, including amantadine, the symptoms significantly improved. This clinical course suggests that polypharmacy, in addition to PD itself, poses a significant risk of delirium and epileptic seizures, even in patients with mild renal dysfunction.

Conclusion: This report is indicative of the risk of polypharmacy and highlights the importance of citing drug interactions for a correct diagnosis in patients presenting with complex symptoms.

KEYWORDS

Parkinson's disease, polypharmacy, delirium, Parkinson's disease psychosis, renal dysfunction

1 Introduction

Parkinson's disease (PD) is characterized by the degeneration of dopaminergic neurons in the substantia Nigra. The condition causes motor symptoms such as rigidity, immobility, and resting tremors, as well as non-motor symptoms, including psychiatric and autonomic symptoms. The prevalence of PD increases with age, reaching a peak at 85–89 years of age, and

is more common in men than in women. Although PD is idiopathic in most patients, genetic and environmental factors are also associated with this disorder (1). The Braak hypothesis is the most widely cited explanation for the neurological progression of PD (2). This hypothesis indicates that PD originates in the dorsal vagal nucleus and olfactory bulb, and progresses to the cerebral cortex, resulting in cognitive deficits and hallucinations, particularly in advanced PD. Therefore, dopamine replacement is now believed to be the most commonly used treatment for PD (1, 3).

In addition to the development of several novel anti-PD medicines, polypharmacy is one of the most crucial medical issues, especially among older individuals (4, 5). Furthermore, both PD and its pharmacological treatment frequently induce psychosis and delirium. Many researchers have extensively discussed the pathogenesis of delirium and epileptic seizures in idiopathic PD. Psychosis rarely occurs, and delusions are less frequent than hallucinations in patients with untreated idiopathic PD (5). Furthermore, hallucinations in idiopathic PD have been identified as multifactorial entities dependent on extrinsic and intrinsic mechanisms, including genetic, anatomical, neurotransmission-mediated, and environmental factors (6). The pathomechanism of hallucinations and delusions in dementia with Lewy bodies is considered identical to that of levodopa-induced psychosis (7). Starr reported that alteration of dopamine neurotransmission is one of the key contributors to the pathogenesis of epileptic seizures. In addition, the proconvulsant properties of selective D1 agonists indicate that dopamine lowers the seizure threshold (8).

We encountered a patient with idiopathic PD (Hoehn and Yahr stage: 3 and Movement Disorder Society Unified Parkinson's Disease Rating Scale: 108), who was originally prescribed dopaminergic medicines. The interaction of these medications with multiple agents may have triggered delirium and epileptic seizures after admission. As we consider this case suggestive, we report it along with a literature review.

2 Case presentation

A man in his 70s came to our hospital complaining of weight loss, anorexia, and dysphagia. His medical history included hypertension and dyslipidemia, in addition to PD. He had mild dementia because his mimimental state examination score was 20. He had been taking medication for PD for 12 years, and his weight loss commenced in the last year of admission, with a loss of 10 kg in the last three months. In October of the same year, fatigue, dizziness, dysuria, and severe constipation developed along with a marked decrease in food intake. A few days before visiting our hospital, he visited a nearby hospital and underwent esophagogastroduodenoscopy and cranial magnetic resonance imaging; however, the results were negative. Blood tests revealed mild renal dysfunction (estimated glomerular filtration rate: 36.9 mL/min/1.73 m^2), mild inflammatory response (C-reactive protein: 1.24 mg/dL), and anemia (hemoglobin: 8.2 g/dL). He was admitted to our hospital for further examination and tests for weight loss, anorexia, and anemia were performed. Upon admission, a general physical examination revealed no significant abnormalities. However, a neurological examination revealed resting tremors, bladder and bowel incontinence, and orthostatic hypotension. In contrast, the mask-like facial appearance and muscle rigidity were very mild, even though his swallowing function significantly declined. He developed epileptic seizures and delirium on the morning of the 3rd day after amantadine and droxidopa was initiated for orthostatic hypotension. The total number of his medicines was 14 then (Table 1). His epileptic seizures were considered as tonic–clonic, although he did not have status epileptics throughout the clinical course. The patient's delirium was considered as a mixed type. Confusion Assessment Method (CAM) short form was applied and his condition met the CAM short form diagnostic criteria (9). The brain magnetic resonance imaging only showed mild cerebral atrophy, and the patient did not have any history of cerebrovascular diseases or seizures in the past. The electroencephalogram showed repetitive sharp waves and spike-and-wave complexes in the left frontal and temporal lobes, but any significant electrolytes imbalances were not observed including serum magnesium (2.3 mg/dL) and no magnesium supplement had been taken. Although the patient showed a mild loss of appetite, he did not have any infections including pneumonia or urinary tract infection. Because these results suggested intoxication from dopaminergic medicines, amantadine and droxidopa were discontinued. After discontinuation of amantadine and droxidopa, we increased the doses of levodopa (600 mg/day) and entacapone (600 mg/day) to 1,000 mg/day for each medicine. After these adjustments, his Parkinsonism was well controlled and no adverse reactions such as epileptic seizure, delusion or delirium were observed for half a year. Furthermore, his anorexia was improved but urinary symptoms or constipation was not changed drastically. In addition, he underwent a total colonoscopy for further examination, but no findings explaining the weight loss or any other issues were identified. Based on the patient's clinical course, we concluded that his multiple manifestations were attributable to polypharmacy, including the use of anti-PD medicines.

TABLE 1 Prescribed medicines.

Drug	Dosage
Amantadine	200 mg/day
Droxidopa	100 mg/day
Istradefylline	40 mg/day
Rasagiline	1 mg/day
Risperidone	1 mg/day
Fenofibrate	160 mg/day
Amlodipine	5 mg/day
Lubiprostone	24 mg/day
Magnesium oxide	1.32 g/day
Mosapride	5 mg/day
Elobixibat	10 mg/day
Sennoside	24 mg/day
Vonoprazan	20 mg/day
Stalevo L100	6 tablets/day (Levodopa 600 mg/day, Entakapon 600 mg/day)

3 Discussion

The prevalence of psychosis in cross-sectional studies of PD is 13–60% depending on the selected diagnostic criteria and specific population. Moreover, the lifetime prevalence of PD is 47–60% (1–3).

PD psychosis affects the quality of life and contributes to physical disability, in addition to increasing caregiver burden and distress (10). The prevalence of psychosis in untreated *de novo* PD was reported to be 3% (11). Additionally, dopamine replacement therapy may be associated with an increased frequency of psychiatric symptoms (12). Psychiatric symptoms, encompassing minor phenomena, visual hallucinations, non-visual hallucinations, delusions, and visual illusions, are particularly common and occur frequently at night in dim lighting conditions. Several differences exist between hallucinations in primary psychiatric disorders and psychosis in PD. For instance, hallucinations in schizophrenia are more frequent and auditory than those in PD psychosis (10). Although the pathophysiology of PD psychosis is intricate and not fully elucidated, most dopaminergic medicines for PD have been observed to induce psychotic symptoms. Consequently, dopamine receptor antagonists are often employed in the treatment of psychosis. Thus, chronic dopaminergic treatment may result in mesolimbic dopamine receptor hypersensitivity, which may contribute to the development of psychosis (13). PD psychosis is also associated with rapid eye movement sleep behavior disorders and sleep abnormalities (14, 15).

Many neurotransmitters, including dopamine, are involved in the development of epilepsy, with dopamine playing an important role in its regulation. The modulation of seizures also depends on the dopamine receptor subtypes and brain regions in which dopamine receptors are activated. Various animal and human studies have demonstrated that D1-like and D2-like receptor signaling exert opposing effects on limbic epileptogenesis. In general, signaling through D1-like receptors promotes epileptogenesis by lowering the threshold and increasing the severity of epileptic seizures (16, 17). In humans, high D1 expression is observed in the neocortex of patients with temporal lobe epilepsy, and D1 binding is positively correlated with the duration of epilepsy (18). In contrast, D2-like receptor signaling is generally considered to possess antiepileptic properties, and antagonizing D2-like receptor signaling lowers the seizure threshold (19, 20). Importantly Gruntz et al. reported that PD is associated with an elevated risk of epileptic seizures, indicating that the adjusted odds ratio of epileptic seizures was 1.68 (95% confidence interval = 1.43–1.98) in patients with PD compared to that in individuals without PD (21).

Today, polypharmacy, which is usually defined as the regular use of five or more drugs, is a very important medical issue, due to its association with drug-related problems, frequent hospital admissions, a high risk of morbidity and mortality, and a high economic burden, including medical bills (22, 23). In an observational study involving Japanese individuals, approximately 75% of participants consumed five or more drugs. The study demonstrated that the number of medicines was associated with the risk of renal failure, cardiovascular events, and mortality (24). According to a study by Naghnaghia et al., older adults with excessive polypharmacy (10 or more agents) were 2.7 times more likely to have renal dysfunction compared to those consuming fewer than five agents (25).

Amantadine acts on the dopaminergic neurons and is used to treat PD (26). In Japan, amantadine is approved and covered by insurance for this purpose owing to its effectiveness in ameliorating reduced spontaneity resulting from cerebral infarction. However, as amantadine is excreted primarily via renal clearance, the half-life of the drug tends to be prolonged in patients with renal dysfunction (27). Although some reports have highlighted amantadine intoxication in patients with advanced renal failure (28, 29), the number of reported cases of amantadine intoxication in patients with mild to moderate renal dysfunction is lower than that in patients with severe renal failure (27–29). Amantadine toxicity primarily affects the central nervous system (CNS) and manifests as hallucinations, confusion, and nightmares. Other CNS manifestations including insomnia, fatigue, drowsiness, acute psychosis, coma, and seizures have also been reported (28, 29). Although the interaction between droxidopa and amantadine has rarely been reported, the balance of neurotransmitters and their interactions should be associated with the pathophysiology. It was reported that amantadine inhibits NMDA receptor and this action has a beneficial effect on PD. It can also disrupt normal brain signaling, which can contribute to confusion and delirium. NMDA receptor inhibition may lower the seizure threshold in some individuals. Amantadine may also have mild anticholinergic properties, which can interfere with the balance of acetylcholine in the brain. This can contribute to cognitive decline and confusion, potentially leading to delirium (28–29). Therefore, regardless of renal function, administering amantadine or other anti-PD medications should be carefully considered, especially in a context of geriatric patients who already experience the issue of polypharmacy.

This patient, who was originally consuming 14 medicines (Table 1), including six anti-PD medicines, presented with seizures and delirium after admission to the hospital. Based on the clinical course, the patient's symptoms were speculated to have occurred due to elevated blood amantadine levels triggered by droxidopa. Considering the patient's moderately impaired renal function, it is improbable that renal function alone caused amantadine intoxication, suggesting that polypharmacy also contributed.

Polypharmacy is a serious issue in older adults, with overmedication leading to many unfavorable events. As multiple medicines regulate the balance of several neurotransmitters in PD, adding one agent could disrupt the homeostasis of the neuronal network. It may be useful to promote deprescribing in the everyday clinical practice rather than adding a medication for a new symptom or an adverse reaction. Considering the aforementioned information, treating patients with the minimum amount of medication whenever feasible is important. To achieve this goal, drug adjustments and prescriptions are recommended. In addition, patients with PD consuming multiple agents are at risk of developing amantadine intoxication due to drug interactions, even if the renal dysfunction is mild to moderate. This report emphasizes the risk of polypharmacy and suggests the importance of citing amantadine intoxication as a differential diagnosis in patients with PD and mild to moderate renal dysfunction who present with symptoms of seizures and/or delirium.

Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

Ethics statement

The studies involving humans were approved by Tohoku Medical and Pharmaceutical University. The studies were

conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study. Written informed consent was obtained from the individual(s) for the publication of any potentially identifiable images or data included in this article.

Author contributions

TaY: Writing – original draft, Data curation. AA: Data curation, Writing – review & editing. SM: Data curation, Writing – review & editing. EK: Data curation, Writing – review & editing. ToO: Data curation, Writing – review & editing. ToY: Writing – review & editing. AI: Data curation, Writing – original draft. JU: Data curation, Writing – review & editing. YF: Writing – review & editing. AK: Writing – review & editing. KS: Writing – review & editing. TaO: Writing – review & editing. KF: Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Bogers JS, Bloem BR, Den Heijer JM. The etiology of Parkinson's disease: new perspectives from gene-environment interactions. *J Parkinsons Dis*. (2023) 13:1281–8. doi: 10.3233/JPD-230250

2. Armstrong MJ, Okun MS. Diagnosis and treatment of Parkinson disease: a review. *JAMA*. (2020) 323:548–60. doi: 10.1001/jama.2019.22360

3. Qu J, Lu J, Hu Y. Research and development of anti-Parkinson's drugs: an analysis from the perspective of technology flows measured by patent citations. *Expert Opin Ther Pat*. (2019) 29:127–35. doi: 10.1080/13543776.2019.1567712

4. de Souza IKC, Rosa-Souza FJ, de Lucena Alves CP, Duhamel TA, Waters DL, Martins RR, et al. Polypharmacy, physical activity, and sedentary time in older adults: a scoping review. *Exp Gerontol*. (2023) 183:112317. doi: 10.1016/j.exger.2023.112317

5. Fernandez HH, Trieschmann ME, Friedman JH. Treatment of psychosis in Parkinson's disease: safety considerations. *Drug Saf*. (2003) 26:643–59. doi: 10.2165/00002018-200326090-00004

6. Rojas M, Chávez-Castillo M, Duran P, Ortega Á, Bautista-Sandoval MJ, Salazar J, et al. Psychosis in Parkinson's disease: looking beyond dopaminergic treatments. *Curr Pharm Des*. (2022) 28:2725–41. doi: 10.2174/1381612828666220428102802

7. Iseki E, Marui W, Nihashi N, Kosaka K. Psychiatric symptoms typical of patients with dementia with Lewy bodies—similarity to those of levodopa-induced psychosis. *Acta Neuropsychiatr*. (2002) 14:237–41. doi: 10.1034/j.1601-5215.2002.140507.x

8. Starr MS. The role of dopamine in epilepsy. *Synapse*. (1996) 22:159–94. doi: 10.1002/(SICI)1098-2396(199602)22:2<159::AID-SYN8>3.0.CO;2-C

9. Jones HT, Davis DH. What you need to know about: delirium in older adults in hospital. *Br J Hosp Med*. (2021) 82:1–10. doi: 10.12968/hmed.2020.0603

10. Schneider RB, Iourinets J, Richard IH. Parkinson's disease psychosis: presentation, diagnosis and management. *Neurodegener Dis Manag*. (2017) 7:365–76. doi: 10.2217/nmt-2017-0028

11. Weintraub D, Simuni T, Caspell-Garcia C, Coffey C, Lasch S, Siderowf A, et al. Cognitive performance and neuropsychiatric symptoms in early, untreated Parkinson's disease. *Mov Disord*. (2015) 30:919–27. doi: 10.1002/mds.26170

12. de la Riva P, Smith K, Xie SX, Weintraub D. Course of psychiatric symptoms and global cognition in early Parkinson disease. *Neurology*. (2014) 83:1096–103. doi: 10.1212/WNL.0000000000000801

13. Chang A, Fox SH. Psychosis in Parkinson's disease: epidemiology, pathophysiology, and management. *Drugs*. (2016) 76:1093–118. doi: 10.1007/s40265-016-0600-5

14. Lee AH, Weintraub D. Psychosis in Parkinson's disease without dementia: common and comorbid with other non-motor symptoms. *Mov Disord*. (2012) 27:858–63. doi: 10.1002/mds.25003

15. Factor SA, Steenland NK, Higgins DS, Molho ES, Kay DM, Montimurro J, et al. Payami H disease-related and genetic correlates of psychotic symptoms in Parkinson's disease. *Mov Disord*. (2011) 26:2190–5. doi: 10.1002/mds.23806

16. Starr MS, Starr BS. Seizure promotion by D1 agonists dose not correlate with other dopaminergic properties. *J Neural Transm*. (1993) 6:27–34. doi: 10.1007/BF02252620

17. Gangarossa G, di Benedetto M, O'Sullivan GJ, Dunleavy M, Alcacer C, Bonito-Oliva A, et al. Convulsant doses of a dopamine D1 receptor agonist result in Erk-dependent increases in Zif268 and arc/Arg3.1 expression in mouse dentate gyrus. *PLoS One*. (2011) 6:e19415. doi: 10.1371/journal.pone.0019415

18. Rocha L, Alonso-Vanegas M, Villeda-Hernández J, Mújica M, Cisneros-Franco JM, López-Gómez M, et al. Borsodi a dopamine abnormalities in the neocortex of patients with temporal lobe epilepsy. *Neurobiol Dis*. (2012) 45:499–507. doi: 10.1016/j.nbd.2011.09.006

19. de Toffol B, Trimble M, Hesdorffer DC, Taylor L, Sachdev P, Clancy M, et al. Kanemoto K pharmacotherapy in patients with epilepsy and psychosis. *Epilepsy Behav*. (2018) 88:54–60. doi: 10.1016/j.yebeh.2018.09.001

20. Channer B, Matt SM, Nickoloff-Bybel EA, Pappa V, Agarwal Y, Wickman J. Gaskill PJ dopamine, immunity, and disease. *Pharmacol Rev*. (2023) 75:62–158. doi: 10.1124/pharmrev.122.000618

21. Gruntz K, Bloechliger M, Becker C, Jick SS, Fuhr P, Meier CR, et al. Parkinson disease and the risk of epileptic seizures. *Ann Neurol*. (2018) 83:363–74. doi: 10.1002/ana.25157

22. Masnoon N, Shakib S, Kalisch-Ellett L, Caughey GE. What is polypharmacy? A systematic review of definitions. *BMC Geriatr*. (2017) 17:230. doi: 10.1186/s12877-017-0621-2

23. Halli-Tierney AD, Scarbrough C, Carroll D. Polypharmacy: evaluating risks and deprescribing. *Am Fam Physician*. (2019) 1:32–8.

24. Kimura H, Tanaka K, Saito H, Iwasaki T, Watanabe S, Kazama S. Association of Polypharmacy with kidney disease progression in adults with CKD. *Clin J Am Soc Nephrol*. (2021) 16:1797–804. doi: 10.2215/CJN.03940321

25. Naghnaghia S, Nazzal Z, Abu Alya L, Al-Ramahi R, Hamdan Z, Samara E, et al. The association between renal impairment and polypharmacy among older Palestinian patients: a multi-center cross-sectional study. *BMC. Prim Care*. (2023) 24:24. doi: 10.1186/s12875-023-02005-9

26. Schwab RS, England AC, Poskanzer DC, Young RR. Amantadine in the treatment of Parkinson's disease. *JAMA*. (1969) 208:1168–70. doi: 10.1001/jama.208.7.1168

27. Okada K, Uno T, Utsumi M, Usui K, Nakamura M, Nakashima I, et al. Amantadine intoxication despite moderate renal dysfunction: a case of combined use with donepezil. *Clin Case Rep*. (2020) 8:1053–6. doi: 10.1002/ccr3.2803

28. Macchio GJ, Ito V, Sahgal V. Amantadine-induced coma. *Arch Phys Med Rehabil*. (1993) 74:1119–20. doi: 10.1016/0003-9993(93)90072-I

29. Nakata M, Ito S, Shirai W, Hattori T. Severe reversible neurological complications following amantadine treatment in three elderly patients with renal insufficiency. *Eur Neurol*. (2006) 56:59–61. doi: 10.1159/000095147

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Translation, cultural debugging, and validation of the Chinese version of the Sour Seven Questionnaire: a cross-sectional study

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Introduction: Intensive care unit delirium (ICUD) is an acute cerebral dysfunction accompanied by a change of level of consciousness, disorientation, and cognitive dysfunction, typically occurring over a short duration ranging from hours to days and resulting from underlying medical causes. Family members may sometimes detect changes in consciousness earlier than medical staff. The Sour Seven Questionnaire is a tool to assist family members in screening for delirium, but there is currently no Chinese version. This study aimed to translate and cross-culturally debug the Sour Seven Questionnaire and test the effectiveness of the Chinese version in screening for ICUD by family members.

Methods: To create the Chinese version of the questionnaire, the questionnaire was first translated and then culturally debugged through expert consultation and cognitive interviews. Patients and their family members admitted to three ICUs in a Chinese hospital were selected to test the Chinese version of the Sour Seven Questionnaire and the results were compared with those of the validated and recommended Confusion Assessment Method for the intensive care unit (CAM-ICU) assessment.

Results: A total of 190 ICU patients and their families were included in this study. Results of the CAM-ICU assessment showed that 73 (38.4%) patients developed ICUD compared to the 66 (34.7%) using the Chinese version of the Sour Seven Questionnaire, which had a Cohen's kappa coefficient of 0.853, a sensitivity of 0.863, and a specificity of 0.974. The positive predictive value was 0.954 and the negative predictive value was 0.919.

Discussion: The Chinese version of the Sour Seven Questionnaire is a valid assessment tool for helping families screen for ICUD, and it is effective in identifying altered consciousness in patients even during online visits.

KEYWORDS

Chinese version, delirium, family member, nursing, Sour Seven Questionnaire

1 Introduction

ICU Delirium (ICUD) is characterized by a disturbance of attention, orientation, and awareness that develops within a short period of time, typically presenting as significant confusion or global neurocognitive impairment, with transient symptoms that may fluctuate depending on the underlying causal condition or etiology (1–3). The incidence rate of ICUD ranges from 33.1 to 80% (1–3). ICUD occurrence in patients increases the risk of hospital-acquired infections and mortality, prolongs hospital stay, and generates higher hospitalization costs (4). ICUD could lead to an increase in hospital costs of $4,654 per patient (5). The cost of delirium treatment in the United States increased from $16 billion (2004) to $182 billion (2021) (6, 7). This shows that ICUD poses a significant challenge to patient health and healthcare resources.

ICU nurses are the healthcare professionals who spend the most time with critically ill patients, being the best personnel to assess ICUD. Guidelines (2, 8) and consensus (1, 9) recommend the CAM-ICU or ICDSC as valid screening tools for ICUD. However, Lange et al. (10) found that 53.1% of ICU nurses had never received education on delirium, 16.4% routinely assessed delirium, 35.8% occasionally assessed delirium, and they rarely used validated scales. A survey from China noted that only 10.81% of ICU nurses were familiar with delirium, 11.49% routinely used a delirium assessment tool to screen for it, and 37.17% assessed patients based on their own experience (11). Family members usually know the patient best and may notice subtle changes in the patient's cognition and behavior earlier than nurses (12). Therefore, family members' involvement in assessing ICUD can assist in early diagnosis and provide valuable time for early intervention. When assessment tools are not used, delirium is often missed diagnosis, with nurses identifying only 35% of delirium cases (13), resulting in many patients with ICUD not being identified. Several family versions of assessment tools have been developed to fully utilize the role of families in delirium assessment (14). However, only the Family Confusion Assessment Method (FAM-CAM) (12) and Sour Seven Questionnaire (15) have been validated for use in ICUD assessment, with the latter proving superior in assessing delirium (12).

Given that patient benefits of conducting an ICUD assessment outweighs the potential risks, family members may be more likely to recognize delirium symptoms than nurses who are unfamiliar with the patient (8, 14). However, there is no Chinese version of this tool for patients' families. Therefore, we aim to culturally debug and clinically apply the Sour Seven Questionnaire to explore its effectiveness in predicting ICUD and lay the foundation for further in-depth research.

2 Materials and methods

2.1 Location

This study was conducted in three ICUs (medical, surgical, and comprehensive) of 30 beds each, of a 4,550-bed hospital in China. This study is reported according to the Standards for the Reporting of Diagnostic Accuracy Studies (STARD) (16). This study was approved by the Ethics Committee of Henan provincial people's hospital (Approval no. 2021-94). This study was registered in the National Information Platform for Universal Health Coverage (NPUHC) medical research registry case information system,[1] (MR-41-22-022684). In this study all participants provided written informed consent prior to recruitment. The accession numbers of data have not yet been obtained at the time of submission, but we can provided the data to reviewer, if it is needed.

2.2 Participants

In this study, a convenience sampling method was used to collect data. The participants of this study were patients admitted to the three ICUs between July 2022 and May 2023. The inclusion criteria were: (1) age ≥ 18 years; (2) ICU stay ≥48 h; (3) RASS score ≥ −2; (4) able to communicate; (5) and agreeing to voluntary participation in this study. Patients were excluded if they presented (1) a history of mental illness and (2) diagnosis of delirium before ICU admission.

In this study, family members were defined as those who lived with the patient or had contact with the patient at least once a month and were familiar with the patient's habits and personality. The inclusion criteria for family members were: (1) age ≥ 18 years old; (2) ability to use a smartphone; (3) ability to participate in visits on time and throughout the entire study period; (4) ability to communicate; and (5) agreeing to voluntary participation in this study.

The sample size assessment was based on sensitivity as the main indicator (17). The predicted sensitivity of the Chinese version of the Sour Seven Questionnaire was 80%, 1-β = 0.9, and ICUD incidence 33.1%. Therefore, the required sample size was 186 cases.

$$n = \left(Z \wedge 2 \times P\left(1-P\right)\right) / \beta \wedge 2 \; N = n / Prevalence$$

$$\left(Z = 1.96,\ P = 0.80,\ \beta = 0.1,\ Prevalence = 0.331\right)$$

2.3 Status of the target scale

The Sour Seven Questionnaire (SSQ) was developed by Shulman et al. (18) and contains seven entries. While it has a total score of 18, patients are at high risk for delirium when they score ≥ 4, and delirium is occurring when they score ≥ 9. The sensitivity of the validation in Canadian ICU patients was 0.64 and specificity 0.85 (18). Furthermore, it has been noted that the SSQ has a positive and negative predictive value of 89.5 and 90%, respectively (14).

2.4 Translation and cross-cultural adaptation process

We obtained the SSQ authorization and adaptation in accordance with ISPOR guidelines (19). Two ICU nurses (Both translators are native Chinese speakers. They hold a master's degree in nursing in Ireland and have significant experience working in intensive care units (ICUs). One translator has 8 years of ICU experience, while the other has 6 years. Their involvement in ICU delirium research is extensive,

1 https://www.medicalresearch.org.cn

having participated in several projects and co-authored papers with the research team) independently completed the translation. The research team leader reviewed the two translations and original scale, discussed inconsistencies, and coordinated revisions to develop a comprehensive Chinese version. This version was presented as accurately as possible in easy-to-understand language based on the meaning of the original scale items. Two master's students who had not read the English version of the SSQ independently reverse translated the Chinese version. The research team leader reviewed both translations and the original scale. The final translation was discussed and approved by the research team core members.

Four ICU medical specialists, three ICU nursing specialists, and the head nurse of the Department of Psychological Medicine were requested to evaluate the content of the entries in the Chinese version of the Sour Seven Questionnaire (CVSSQ). The appropriateness of each scale entry was evaluated using a 5-point Likert scale (1 = "not at all appropriate" and 5 = "very appropriate"). For entries with scores of 1–3, the experts were requested to provide modification suggestions, while the research team discussed and developed the CVSSQ. The modified scale was sent back to the eight experts for a second round of consultation until consensus was reached.

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2.5 Pre-survey

A total of 30 pairs of family members and patients who met the inclusion and exclusion criteria were recruited to use the CVSSQ in the pretest phase. After the family members assessed the patients, they were interviewed by the researcher to collect their opinions on the tool. Modifications were made based on their opinions.

2.6 Delirium assessment

The CAM-ICU has a good diagnostic ability for delirium and can be conducted rapidly (8). Trained nurses used it as a diagnostic tool for delirium.

2.7 Data collection

2.7.1 Nurses grouping and training

As each ICU contained four nursing groups, we recruited one nurse in each group (12 nurses in total) responsible for assisting family members to conduct online visits (RT1). Simultaneously, we recruited another nurse in each nursing group (12 nurses in total) who were proficient in using the CAM-ICU to be responsible for assessing delirium (RT2). After completing their training, the RT2 nurses first underwent a theoretical examination. Once they passed the theoretical examination, the nurses were required to evaluate standardized patients using the CAM-ICU to demonstrate their proficiency in using the CAM-ICU correctly. Upon passing these assessments, the RT2 nurses were eligible to participate in the study.

2.7.2 Family-administered delirium assessments

When patients who met the inclusion and exclusion criteria were admitted to the ICU, the nurse from RT1 was responsible for obtaining informed consent from the family and the patient. This nurse informed the family that only one member could participate in this study and gave a paper copy of the CVSSQ to the family before each online visit. Because the Sour Seven Questionnaire is a novel, brief, easy-to-use clinical tool, we did not have training for the families (20). The nurses from RT1 assisted the family with a 20-min online visit daily from 10:00 to 11:00 and 21:00 to 22:00 every day. During the visit, the family assessed the patient using the CVSSQ, and the results were maintained by the RT1. In this study, a CVSSQ score of ≥9 points is the screening criterion for ICUD positivity (20). When the family used the CVSSQ to assess whether the patient had an ICUD, a score of <9 was classified as ICUD-negative, while a score of 9 or greater was classified as ICUD-positive. When the family is unable to determine whether the patient's performance aligns with what is described on the CVSSQ, we consider the assessment to be "inconclusive" (see Figure 1).

2.7.3 Clinical delirium assessments

One hour after the family's visit, the nurses from RT2 assessed the patient for delirium using the CAM-ICU. The results of CAM-ICU were maintained by the RT2. The RT1 and RT2 were unaware of each other's delirium assessment results.

2.7.4 Stopping the assessment

The assessment was stopped when the patient was transferred out of the ICU, or diagnosed with delirium by the CAM-ICU or CVSSQ. For example, when a patient has a CAM-ICU score of 4 but a CVSSQ score of 3, the assessment can be stopped. At this point, the patient is considered to have been assessed with a positive CAM-ICU and a negative CVSSQ result.

2.7.5 Quality control

Each week, one investigator who is skilled in the use of the CAM-ICU reassessed the patient using the CAM-ICU within 1 h of the end of the assessment for RT2. The assessment of RT2 was considered valid if the results were consistent; if they differed, another investigator who was skilled in the use of the CAM-ICU performed the assessment.

2.8 Statistical analysis

Statistical analysis was performed using IBM SPSS Statistics for Windows, Version 26.0 (IBM Corp). Data that did not follow a normal distribution are reported as medians [interquartile range] and count data are expressed as percentages. Validity analyses were conducted using the item-level content validity index (I-CVI), scale-level content validity index (S-CVI), and diagnostic validity. The reliability analysis was validated using the Cohen's kappa coefficient and inter-rater reliability. Sensitivity, specificity and positive and negative predictive values for the CVSSQ were calculated using crosstabs. The area under the receiver operating characteristic curve (AUROC) AUROC was used to analyze the ability of delirium detection for the CVSSQ. When mapping the AUROC, the screening results for delirium were converted into binary variable: CAM-ICU-positive (≥4 points), CAM-ICU-negative (<4

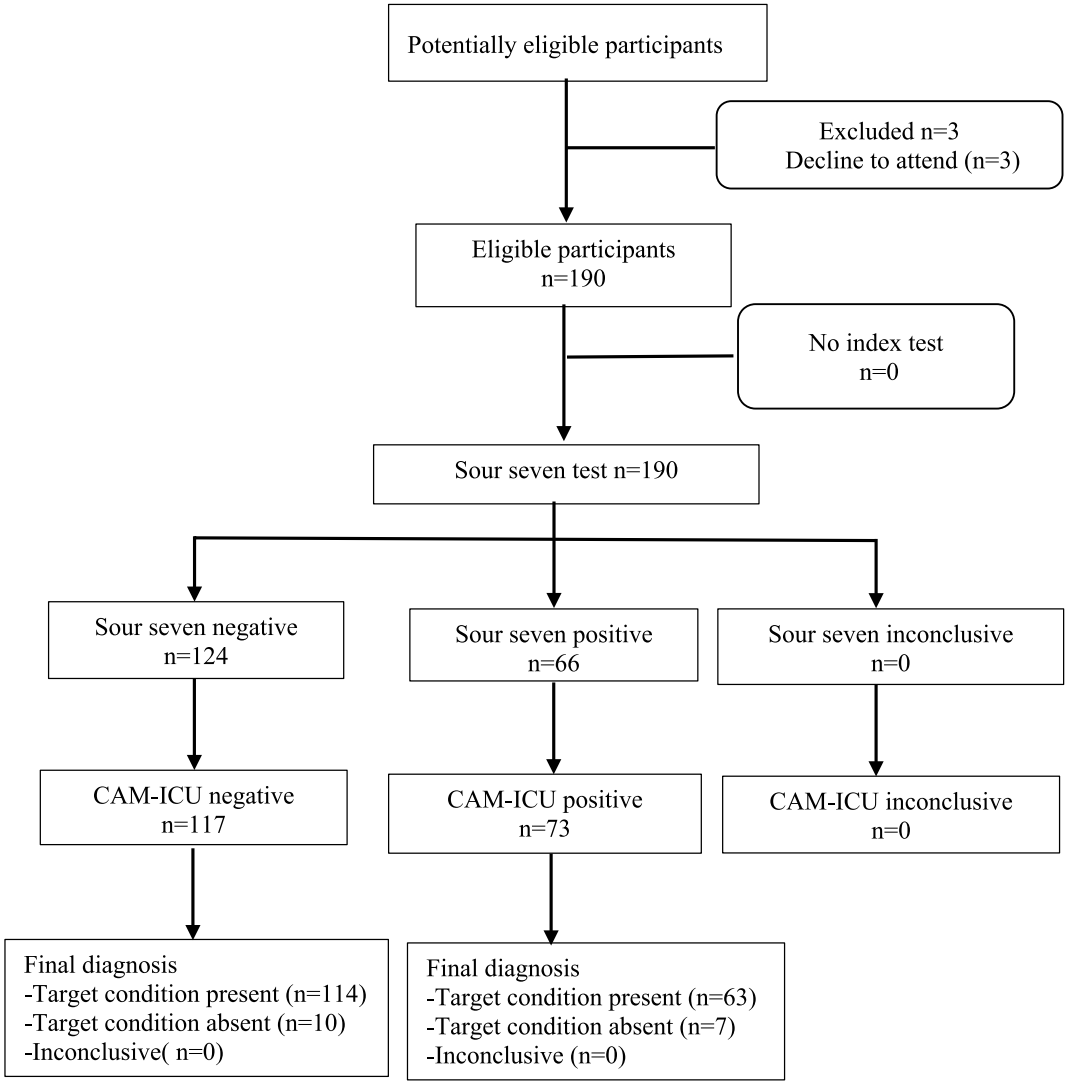

FIGURE 1
Flow diagram of participants.

points); and CVSSQ-positive (≥9 points), CVSSQ-negative (<9 points). The CAM-ICU results were used as the status variable. Differences were considered statistically significant at $p < 0.05$.

3 Results

This study included 190 patients, of whom 73 (38.4%) developed ICUD (see Figure 1). Patients' median age was 55 [47, 63] years, 99 (52.1%) were male, and 108 (56.8%) were medical patients while 82 (43.2%) were surgical (see Table 1). The family members' age averaged at 51 [42, 59] years old, and 101 (53.2%) were male (see Table 2).

3.1 Validity

3.1.1 Content validity

After being scored by the eight experts, the CVSSQ used in this study had an I-CVI and S-CVI score of one for each entry.

3.1.2 Diagnostic validity

Cohen's kappa coefficient of the CVSSQ and CAM-ICU diagnostic results in this study was 0.853 (95% CI 0.777–0.929, $p < 0.01$). The sensitivity, specificity, positive, and negative predictive values of the CVSSQ were 0.863, 0.974, 0.954, and 0.919, respectively (see Table 3). The AUROC for the CVSSQ was 0.919 (95% CI 0.869–0.969, $p < 0.01$; Figure 2).

3.2 Reliability confidence

Cohen's kappa coefficient between the CVSSQ and CAM-ICU assessment results was 0.853 ($p < 0.01$).

4 Discussion

We used the CAM-ICU as a diagnostic criterion because it is a tool for assessing delirium in the ICU that is widely used in clinical

TABLE 1 General information of ICU patients.

Items	Delirium $N = 73$	Non-delirium $N = 117$	Value	P
Gender (female), *n* (%)	28 (38.6)	63 (53.8)	190.000[a]	<0.01
Age, year (Age, median [IQR])	62 [52, 68]	53 [45, 60]	4.621[b]	<0.01
Marital status, *n* (%)			8.577[c]	0.02
Single	0	4 (3.4)		
Married	65 (89.0)	107 (91.5)		
Divorced	2 (2.8)	5 (4.3)		
Widowed	6 (8.2)	1 (0.8)		
Category of disease			9.988[a]	<0.01
Medical patients, *n* (%)	31 (42.5)	77 (65.8)		
Surgical patient, *n* (%)	42 (57.5)	40 (34.2)		

[a]Chi-square test. [b]Mann–Whitney *U* test. [c]Fisher test.

TABLE 2 General information of family members.

Items	Delirium $N = 73$	Non-delirium $N = 117$	Value	*p*-value
Gender (female), *n* (%)	40 (54.8)	49 (41.9)	3.011[a]	0.10
Age, year (Age, median [IQR])	53 [42, 59]	50 [41, 57]	1.482[b]	0.14
Relationship to ICU patient, *n* (%)			8.072[c]	0.03
Spouse	48 (65.7)	92 (78.6)		
Child	21 (28.8)	16 (13.7)		
Parents	1 (1.4)	6 (5.1)		
Others	3 (4.1)	3 (2.6)		
Education attainment			5.844[a]	0.12
Primary school	19 (26.0)	18 (15.4)		
Junior high school	27 (37.0)	36 (30.8)		
Senior high school	17 (23.3)	39 (33.3)		
Bachelor degree or above	10 (13.7)	24 (20.5)		
Job style, *n* (%)			2.564[a]	0.64
Medical staff	6 (8.2)	5 (4.3)		
Worker	18 (24.7)	27 (23.1)		
Peasants	26 (35.6)	37 (31.6)		
Office worker	9 (12.3)	19 (16.2)		
Other occupation	14 (19.2)	29 (24.8)		
Marital status, *n* (%)			2.940[c]	0.15
Single	0	3 (2.6)		
Married	72 (98.6)	114 (97.4)		
Divorced	0	0		
Widowed	1 (1.4)	0		
Frequency of contact with ICU patient, *n* (%)			0.468[a]	0.494
Direct contact at least once a month	7 (9.6)	8 (6.8)		
Living together	66 (90.4)	109 (83.2)		

[a]Chi-square test. [b]Mann–Whitney *U* test. [c]Fisher test.

practice and has been co-recommended by multiple guidelines (1, 2, 8). In this study, the CVSSQ had a sensitivity and specificity of 0.863 and 0.974, respectively, while Moss (18) study showed a sensitivity and specificity of 0.64 and 0.85, respectively. This may be related to the difference in the frequency of assessment between the two studies. In Moss (18) study, family members conducted only one delirium

TABLE 3 Diagnostic validity of the Chinese version of the Sour Seven Questionnaire.

		CAM-ICU		
		Positive	Negative	Total
CVSSQ	Positive	63	3	66
	Negative	10	114	124
	Total	73	117	190

CAM-ICU, Confusion assessment method of intensive care unit; CVSSQ, The Chinese version of the Sour Seven Questionnaire.

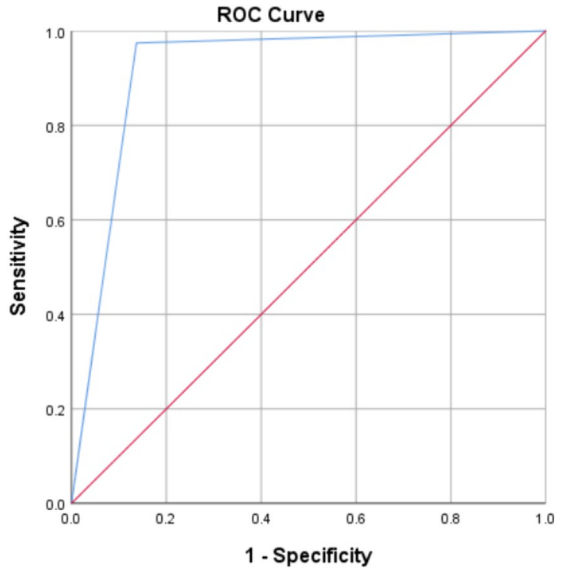

FIGURE 2
ROC curve of the Chinese version of the Sour Seven Questionnaire to predict ICU delirium.

assessment, whereas in this study, family members conducted two in accordance with the nurses' assessments in order to maximize the timely identification of ICUD. Another possible reason for the difference in sensitivity between the two studies may be the fluctuating and rapid nature of delirium presentation (8). Additionally, patient sedation scores were not reported in Moss (18) study. The PADIS guidelines state that the depth of a patient's sedation may lead assessors to make incorrect judgments: the deeper the patient's sedation, the greater the chance of being misjudged (8). We believe that increasing the frequency of family members assessing the patient to be close to the frequency and duration of nurses' assessments better reflects the true effect of family members using the CVSSQ to assess ICUD. Therefore, we consider this to be one of this study's innovations.

The study period coincided with the COVID-19 pandemic; therefore, new cases of coronavirus-related pneumonia were admitted. To avoid aggravating the condition of critically ill patients in the ICU, on-site patient visits were not permitted, and many hospitals used online or telephonic visits to meet the emotional needs of patients and their families (21, 22). Compared to telephonic visits, online visits (via video) can calm patients' emotions through real-time images, reduce the incidence of ICUD, and increase communication between patients and their families (23). Furthermore, online visits reduce the visiting costs and removes traveling barriers (23). In our study, we found that during online visits, family members could assist in diagnosing ICUD by observing the patient's movements. This, to a certain extent, improves the chances of early diagnosis. Online visits not only reduce the risk of infection and difficulty for family members to accompany the patient, but it is also more convenient. While online visitation offers certain benefits, it also presents limitations. One study found a 74% agreement between online and in-person diagnoses and a 79.8% concordance in treatment plans (24). However, the lack of direct interaction with the patient may hinder the accuracy of screening tools like the CVSSQ. This aspect requires further investigation in future studies.

Furthermore, we analyzed whether general patient and family information affected delirium assessment using the CVSSQ. In the patient data analysis, there were differences between patients in the delirium group and those in the non-delirium group in terms of age, gender, marital status, and disease category ($p < 0.05$). The propensity of older age (1, 8), disease category (surgical patients) (1, 25), and marital status (26, 27) to induce ICUD has been demonstrated in several guidelines and studies. Whether gender can induce delirium is inconclusive. However, a study of diabetic patients undergoing coronary artery surgery showed that the risk of delirium was higher in men than in women (28). In a study conducted by Kotfis et al. (29) it was also demonstrated that the risk of delirium was higher in male critically ill patients than in females. Peckham et al. (30) concluded that males have a higher likelihood of bacterial, viral, and other infections; that females have a stronger humoral immune response than males; and that males show an age-related tendency for a decline in B-cells and accelerated immune senescence. The above reasons may contribute to the fact that male are more prone to inflammatory responses. Inflammatory response is one of the important factors that induce ICUD (31, 32).

Family members are the primary users of the CVSSQ, and their perceptions can influence the results of the CVSSQ assessment. Therefore, we recommend more focus on the analysis of family information. The difference in the category of family members in this study was statistically significant ($p = 0.03$), which may be related to spouses who lived together for a longer period having a better understanding of each other. Although the differences in education and occupation between the two groups of family members were not statistically significant ($p > 0.05$), they still suggest that the CVSSQ can be applied to family members with different education levels and professions, which has been less addressed in previous studies.

In this study, we excluded patients with RASS scores <−2. The PADIS guideline states that sedation level may influence the assessment of delirium, noting that many patients with a RASS score of-3 are considered "unassessable" and that the rate of positive delirium is significantly higher when patients have a RASS of-2 (as opposed to a RASS of −1 to 0) (8). Because delirium can manifest as a reduced level of arousal, families typically lack the medical knowledge to easily classify altered consciousness due to sedation as ICUD, thus making the CVSSQ diagnosis less effective (8). Chinese experts believe that "the eCASH concept" is effective in improving patients' comfort and reducing the incidence of ICUD (9). The eCASH concept recommends that light sedation should leave the patient in a state of calmness, comfort, and cooperation (33). Ideally, the patient should be awake to maintain eye contact, interact with caregivers and family members, and participate in physical and/or occupational therapy while being allowed to drift off to sleep when undisturbed (33). This state is broadly equivalent to a Richmond Agitation Sedation Scale (RASS) score of −1 to 0 (33).

The occurrence of ICU delirium increases the risk of hospital-acquired infections and mortality in critically ill patients, prolongs hospital stays, and leads to higher hospitalization costs (4). However, public awareness of delirium lags far behind other important public health issues (32). The prevalence of ICUD in this study was 38.4%, indicating a high prevalence of ICUD in critically ill patients and reflecting the significant use of healthcare resources by ICUD. The PADIS guideline states that early detection of ICUD is essential to expedite clinical assessment and intervention, and ICU nurses are always with the patient, making them the best people to detect ICUD (8). However, several studies have shown that the ability of some ICU nurses to assess delirium does not meet clinical needs due to a lack of knowledge or inadequate training This has led to a large number of patients with ICUD being underdiagnosed in the clinic (34, 35). As the study progressed, the researchers found that family members were able to identify patients with ICU delirium earlier than healthcare professionals; that is, family members were able to recognize patients with ICU delirium earlier (14). This may be related to the fact that family members are more familiar with the patient's habits than healthcare professionals. We translated the SSQ into Chinese and applied it to ICU patients, finding that family members can conduct delirium screening alongside healthcare professionals. Allowing family members to participate in the assessment of ICUD can improve the detection rate of delirium and is a tremendous help in achieving early identification of ICUD in the clinical setting (14). Rosgen et al. (14) suggested that family participation in ICUD assessment can help reduce negative emotions such as anxiety and depression in family members, but this still needs to be confirmed by further studies. In summary, family participation in ICUD detecting is important for addressing the emotional needs of patients and their families, as well as for assisting healthcare professionals in achieving the early identification of delirium.

In this study, we translated the Sour Seven Questionnaire into Chinese and assessed its clinical effectiveness. While our findings suggest that the CVSSQ can help families identify early ICUD, the study was limited to a single center and relied on online visits. With the increasing return to in-person assessments in hospitals, we plan to expand our research into a multicenter study. This study will involve ICUs from various regional hospitals in China and will focus on how different demographics and the mode of consultation influence the effectiveness of delirium detection.

5 Limitations

This study has four limitations. (1) The Diagnostic and Statistical Manual of Mental Disorders (DSM) was not used as a diagnostic criterion for ICUD which may have led to some biased results. However, using the CAM-ICU for delirium assessment is more in line with clinical practice. (2) Because we had previously used the ICUD risk prediction model to assess delirium risk in critically ill patients, we did not validate that a CVSSQ score of ≥4 was the high-risk cut-off point for ICUD; however, we validated that a patient scoring ≥9 could be diagnosed with delirium. (3) The absence of standardized training for families on the Chinese version of the Sour Seven Questionnaire (CVSQQ) in this study may have introduced variability in how families interpreted the questionnaire. This inconsistency could have impacted the accuracy of the assessment results. (4) Although we confirmed the absence of psychiatric abnormalities in patients by reviewing their medical records upon ICU admission, the lack of standardized baseline mental health and cognitive assessments remains a potential limitation. This absence of objective evaluation could influence the accuracy of subsequent assessments.

6 Conclusion

This study demonstrated that the CVSSQ provides a valid assessment of ICUD. It is easy to use and convenient to operate, while potentially playing a significant role in the early identification of ICUD. For an efficient assessment, it is important to promote cooperation between nurses and their families.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by the Ethics Committee of Henan Provincial People's Hospital. The studies were conducted in accordance with the local legislation and institutional requirements. The participants provided their written informed consent to participate in this study.

Author contributions

SZ: Conceptualization, Writing – original draft, Investigation. SL: Methodology, Software, Visualization, Writing – original draft. LL: Project administration, Supervision, Writing – review & editing. HX: Conceptualization, Investigation, Writing – review & editing. MX: Data curation, Investigation, Writing – review & editing. GD: Investigation, Writing – original draft.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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References

1. Medical AONA. Chinese experts consensus on diagnosis and treatment of delirium in general hospital (2021) [guideline]. *Chin J Geriatr*. (2021) 40:1226–33. doi: 10.3760/cma.j.issn.0254-9026.2021

2. Seo Y, Lee HJ, Ha EJ, Ha TS. 2021 KSCCM clinical practice guidelines for pain, agitation, delirium, immobility, and sleep disturbance in the intensive care unit. *Acute Crit Care*. (2022) 37:1–25. doi: 10.4266/acc.2022.00094

3. Stollings JL, Kotfis K, Chanques G, Pun BT, Pandharipande PP, Ely EW. Delirium in critical illness: clinical manifestations, outcomes, and management. *Intensive Care Med*. (2021) 47:1089–103. doi: 10.1007/s00134-021-06503

4. Xing H, Zhou W, Fan Y, Wen T, Wang X, Chang G. Development and validation of a postoperative delirium prediction model for patients admitted to an intensive care unit in China: a prospective study. *BMJ Open*. (2019) 9:e030733. doi: 10.1136/bmjopen-2019-030733

5. Vasilevskis EE, Chandrasekhar R, Holtze CH, Graves J, Speroff T, Girard TD, et al. The cost of ICU delirium and coma in the intensive care unit patient. *Med Care*. (2018) 56:890–7. doi: 10.1097/mlr.0000000000000975

6. Sinvani L, Delle SC, Laumenede T, Patel V, Ardito S, Ilyas A, et al. Improving delirium detection in intensive care units: multicomponent education and training program. *J Am Geriatr Soc*. (2021) 69:3249–57. doi: 10.1111/jgs.17419

7. Milbrandt EB, Deppen S, Harrison PL, Shintani AK, Speroff T, Stiles RA, et al. Costs associated with delirium in mechanically ventilated patients. *Crit Care Med*. (2004) 32:955–62. doi: 10.1097/01.ccm.0000119429.16055.92

8. Devlin JW, Skrobik Y, Gelinas C, Needham DM, Slooter A, Pandharipande PP, et al. Clinical practice guidelines for the prevention and Management of Pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med*. (2018) 46:e825–73. doi: 10.1097/ccm.0000000000003299

9. Tang B, Wang XT, Chen WJ, Zhu SH, Chao YG, Zhu B, et al. Experts consensus on the management of delirium in critically ill patients. *Chin J Intern Med*. (2019) 58:108–18. doi: 10.3760/cma.j.issn.0578-1426.2019.02.007

10. Lange S, Medrzycka-Da BW, Tomaszek L, Wujtewicz M, Krupa S. Nurses' knowledge, barriers and practice in the care of patients with delirium in the intensive care unit in Poland-a cross-sectional study. *Front Public Health*. (2023) 11:1119526. doi: 10.3389/fpubh.2023.1119526

11. Feng Y, Yang F, Fangyu Y. The investigation of ICU nurses cognition and practice of delirium assessment. *J Nurs Adm*. (2019) 19:584–7. doi: 10.3969/j.issn.1671-315x.2019.08.012

12. Krewulak KD, Bull MJ, Wesley EE, Davidson JE, Stelfox HT, Fiest KM. Effectiveness of an intensive care unit family education intervention on delirium knowledge: a pre-test post-test quasi-experimental study. *Can J Anaesth*. (2020) 67:1761–74. doi: 10.1007/s12630-020-01810-5

13. Mart MF, Williams RS, Salas B, Pandharipande PP, Ely EW. Prevention and Management of Delirium in the intensive care unit. *Semin Respir Crit Care Med*. (2021) 42:112–26. doi: 10.1055/s-0040-1710572

14. Rosgen B, Krewulak K, Demiantschuk D, Ely EW, Davidson JE, Stelfox HT, et al. Validation of caregiver-centered delirium detection tools: a systematic review. *J Am Geriatr Soc*. (2018) 66:1218–25. doi: 10.1111/jgs.15362

15. Fiest KM, Krewulak KD, Ely EW, Davidson JE, Ismail Z, Sept BG, et al. Partnering with family members to detect delirium in critically ill patients. *Crit Care Med*. (2020) 48:954–61. doi: 10.1097/ccm.0000000000004367

16. Cohen JF, Korevaar DA, Altman DG, Bruns DE, Gatsonis CA, Hooft L, et al. STARD 2015 guidelines for reporting diagnostic accuracy studies: explanation and elaboration. *BMJ Open*. (2016) 6:e012799. doi: 10.1136/bmjopen-2016-012799

17. He S, Wang Y, Zuo Z. Clinical application of the Chinese version of Cornell assessment of pediatric delirium: a pilot study. *Zhonghua er ke za zhi = Chin J Pediatr*. (2019) 57:344–9. doi: 10.3760/cma.j.issn.0578-1310.2019.05.006

18. Moss SJ, Hee LC, Doig CJ, Whalen-Browne L, Stelfox HT, Fiest KM. Delirium diagnosis without a gold standard: evaluating diagnostic accuracy of combined delirium assessment tools. *PLoS One*. (2022) 17:e0267110. doi: 10.1371/journal.pone.0267110

19. Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, et al. Principles of good practice for the translation and cultural adaptation process for patient-reported outcomes (PRO) measures: report of the ISPOR task force for translation and cultural adaptation [guideline; journal article]. *Value Health*. (2005) 8:94–104. doi: 10.1111/j.1524-4733.2005.04054.x

20. Shulman RW, Kalra S, Jiang JZ. Validation of the sour seven questionnaire for screening delirium in hospitalized seniors by informal caregivers and untrained nurses. *BMC Geriatr*. (2016) 16:44. doi: 10.1186/s12877-016-0217-2. PMID 26879927

21. Fritz C, Claude LA, Hamada S, Trosdorf M, de la Barre H, Yavchitz A, et al. Daily telephone call during the COVID-19 pandemic: perceptions of families and providers. *Am J Crit Care*. (2022) 31:77–81. doi: 10.4037/ajcc2022797

22. Terzi B, Polat S, Banu KH, Kiraner E, Kol E. Determination of patients' family members' needs and related factors in the intensive care unit with visiting restrictions during the COVID-19 pandemic. *Intensive Crit Care Nurs*. (2022) 73:103295. doi: 10.1016/j.iccn.2022.103295

23. Wang J, Qin J, Tung TH, Chen J, Zheng N, Lu L, et al. Impact of the "WeChat cloud service" option for patients in an emergent intensive care unit during an epidemic in Tai Zhou China. *Front Med*. (2021) 8:833942. doi: 10.3389/fmed.2021.833942

24. Verma N, Buch B, Taralekar R, Acharya S. Diagnostic concordance of telemedicine as compared with face-to-face Care in Primary Health Care Clinics in rural India: randomized crossover trial. *JMIR Form Res*. (2023) 7:e42775. doi: 10.2196/42775

25. Aldecoa C, Bettelli G, Bilotta F, Sanders RD, Spies CD, Aceto P, et al. Update of the European society of anaesthesiology and intensive care medicine evidence-based and consensus-based guideline on postoperative delirium in adult patients. *Eur J Anaesthesiol*. (2023) 41:81–108. doi: 10.1097/EJA.0000000000001876

26. Choi NY, Kim EH, Baek CH, Sohn I, Yeon S, Chung MK. Development of a nomogram for predicting the probability of postoperative delirium in patients undergoing free flap reconstruction for head and neck cancer. *Eur J Surg Oncol*. (2017) 43:683–8. doi: 10.1016/j.ejso.2016.09.018

27. Tai S, Xu L, Zhang L, Fan S, Liang C. Preoperative risk factors of postoperative delirium after transurethral prostatectomy for benign prostatic hyperplasia. *Int J Clin Exp Med*. (2015) 8:4569–74.

28. Wang F, Mei X. Association of blood glucose change with postoperative delirium after coronary artery bypass grafting in patients with diabetes mellitus: a study of the MIMIC-IV. *Front Endocrinol*. (2024) 15:1400207. doi: 10.3389/fendo.2024.1400207

29. Kotfis K, Witkiewicz W, Szylinska A, Witkiewicz K, Nalewajska M, Feret W, et al. Delirium severely worsens outcome in patients with COVID-19-a retrospective cohort study from temporary critical care hospitals. *J Clin Med*. (2021) 10:2974. doi: 10.3390/jcm10132974

30. Peckham H, de Gruijter NM, Raine C, Radziszewska A, Ciurtin C, Wedderburn LR, et al. Male sex identified by global COVID-19 meta-analysis as a risk factor for death and ITU admission. *Nat Commun*. (2020) 11:6317. doi: 10.1038/s41467-020-19741-6

31. Oh TK, Park HY, Song IA. Factors associated with delirium among survivors of acute respiratory distress syndrome: a nationwide cohort study. *BMC Pulm Med*. (2021) 21:341. doi: 10.1186/s12890-021-01714-0

32. Wilson JE, Mart MF, Cunningham C, Shehabi Y, Girard TD, MacLullich AMJ, et al. Delirium. *Nat Rev Dis Primers*. (2020) 6:90. doi: 10.1038/s41572-020-00223-4

33. Vincent JL, Shehabi Y, Walsh TS, Pandharipande PP, Ball JA, Spronk P, et al. Comfort and patient-centred care without excessive sedation: the eCASH concept. *Intensive Care Med*. (2016) 42:962–71. doi: 10.1007/s00134-016-4297-4

34. Li X, Zhang L, Gong F, Ai Y. Incidence and risk factors for delirium in older patients following intensive care unit admission: a prospective observational study. *J Nurs Res*. (2020) 28:e101. doi: 10.1097/jnr.0000000000000384

35. Burton JK, Craig L, Yong SQ, Siddiqi N, Teale EA, Woodhouse R, et al. Should video laryngoscopy or direct laryngoscopy be used for adults undergoing endotracheal intubation in the pre-hospital setting? A critical appraisal of a systematic review. *Cochrane Database Syst Rev*. (2021) 15:255–9. doi: 10.1002/14651858

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Delirium following mechanical thrombectomy for ischemic stroke – individuals at risk, imaging biomarkers and prognosis

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Aim: Post-stroke-delirium has been linked to worse outcome in patients with acute cerebrovascular disease; identification of individuals at risk may prevent delirium and thereby improve outcome. We investigate prognosis and factors associated with post-stroke-delirium in patients with large vessel occlusion (LVO) ischemic stroke treated by mechanical thrombectomy (MT).

Methods: 747 patients (53.4% female) prospectively enrolled in the Gutenberg-Stroke-Study from May 2018–November 2022 were analyzed with regard to diagnosis of delirium. Group comparison of patient-, stroke- and treatment characteristics as well as computed tomography(CT)-imaging based parameters of cerebral atrophy (global cortical atrophy [GCA], posterior atrophy [Koedam], medial temporal lobe atrophy [MTA] scores) and white matter lesions (Fazekas score) was conducted. Independent predictors of delirium and the association of delirium with functional outcome at 90-day follow-up was investigated by multiple logistic regression analyses.

Results: We report 8.2% of patients (61/747) developing delirium following MT of LVO. Independent predictors were older age (aOR[95%CI] per year: 1.034[1.005–1.065], $p = 0.023$), male sex (aOR[95%CI]: 2.173[1.182–3.994], $p = 0.012$), general anesthesia during MT (aOR[95%CI]: 2.455[1.385–4.352], $p = 0.002$), infectious complications (aOR[95%CI]: 1.845[1.031–3.305], $p = 0.039$), "other determined" etiology of stroke (aOR[95%CI]: 2.424[1.100–5.345], $p = 0.028$), and a MTA score exceeding age-specific cut-offs (aOR[95%CI]: 2.126[1.065–4.244], $p = 0.033$). Delirium was independently associated with worse functional outcome (aOR[95%CI]: 2.902[1.005–8.383], $p = 0.049$) at 90-day follow-up.

Conclusion: Delirium is independently associated with worse functional outcome after MT of LVO, stressing the importance of screening and preventive measures. Besides conventional risk factors, pathological MTA scores and use of general anesthesia during MT may be easy-to-apply criteria to identify individuals at risk of delirium and implement prevention strategies.

KEYWORDS

stroke, mechanical thrombectomy, endovascular stroke therapy, delirium, atrophy, complications, prognosis

Introduction

Mechanical thrombectomy (MT) is a highly effective treatment for major ischemic stroke due to large vessel occlusion (LVO) and is now the standard of care for acute stroke treatment. However, patients who have suffered a major stroke are a group at high risk for developing complications during hospital stay (Shaw et al., 2019). A common complication in acute stroke patients is delirium, a syndrome characterized by an altered level of consciousness, disorganised thoughts or disorientation, psychomotor disturbances and circadian dysrhythmia, typically with acute onset and fluctuations over time. Delirium in stroke patients has been reported to be associated with worse outcomes (Shi et al., 2012).

Since treatment options are limited, delirium prevention is the goal for hospitalized patients. While interdisciplinary multicomponent interventions have proven effective for delirium prevention in the hospital setting (Burton et al., 2021), identification of individuals at risk of developing delirium may help to design more efficient and targeted preventive measures and enable timely diagnosis of delirium. Etiology of delirium is multifactorial and reports on risk factors vary throughout the literature with sometimes conflicting conclusions. Patient characteristics, including older age and premorbid cognitive decline; stroke characteristics, e.g., stroke location and severity; and further factors, such as infections, have all been reported to be associated with development of delirium in stroke patients (Rhee et al., 2022; Oldenbeuving et al., 2011; Hahn et al., 2023). Although clinical screening instruments for delirium in hospitalized patients have been developed, questions have been raised about their validity in patients with neurological deficits (Vater et al., 2024). Therefore, identification of risk factors and development of predictive tools may help to prevent and diagnose delirium in patients hospitalized due to acute stroke. The few predictive instruments that have been specifically developed for stroke patients largely remain to be externally validated (Drozdowska et al., 2021). Moreover, existing studies originate from mixed stroke cohorts, which predominantly consist of non-major stroke patients and include also patients with hemorrhagic stroke (Oldenbeuving et al., 2014). However, patients with LVO treated by MT constitute a distinct subgroup of stroke patients; data on delirium in these patients is sparse. These patients are poorly represented in published analyses of delirium, as mixed stroke cohorts contain few cases of MT or analyses were conducted before the era of MT as standard therapy for LVO (Shaw et al., 2019).

We investigate the association of patient-, stroke- and treatment characteristics with the development of delirium in a cohort of patients with LVO who were treated by MT. Additionally, we explore the role of easily obtainable imaging biomarkers of cerebral atrophy and white matter lesions (WML) arising from native computed tomography (CT) as a potential independent risk factor for developing delirium. Finally, we analyze whether delirium is an independent predictor for functional outcome three months after MT of LVO.

Methods

Study cohort and outcome parameters

The Gutenberg-Stroke-Study is an ongoing monocentric, prospective, observational study that consecutively enrolls adult patients diagnosed with acute ischemic stroke in our certified German University Hospital stroke center. All 747 patients with LVO treated by MT enrolled in the Gutenberg-Stroke-Study from May 2018 to November 2022 were included in our primary analysis. Baseline demographics, cardiovascular comorbidities, clinical and procedural information as well as clinical follow-up after 90 days (carried out by standardized telephone interview) are recorded. At 90-day follow-up, good functional outcome was defined as modified Rankin Scale score (mRS) $\leq$2 or mRS equal to premorbid mRS in case of premorbid mRS >2. Excellent functional outcome was defined as mRS $\leq$1 or mRS equal to premorbid mRS in case of premorbid mRS >1. Cognitive outcome was evaluated by telephone-based Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). Patients in our comprehensive stroke center are screened for delirium three times a day by stroke-unit nurses on the basis of the Nursing Delirium Screening Scale (NU-DESC) (Lütz et al., 2008) as specified in the local standard operating procedure. Diagnosis of delirum was then obained by the treating stroke-unit physician. We extracted diagnosis of delirium during the hospital stay based on diagnosis as classified by the International Statistical Classification of Disease and related health problems – 10th revision (ICD-10) used for financial reimbursement from the healthcare providers. Possible confounders of delirium (premorbid dementia; acute infections such as pneumonia, urinary tract infection and/or sepsis) were also extracted by diagnosis as classified by the ICD-10.

Standard protocol approval and data availability

Study protocols and procedures were conducted in compliance with the Declaration of Helsinki and in accordance with local ethical guidelines. The Gutenberg-Stroke-Study was approved by the responsible ethics committee of the Landesärztekammer Rheinland-Pfalz (approval number: 2018-13335-Epidemiologie). Written informed consent was obtained from all participants (or guardians of participants). The Gutenberg-Stroke-Study is registered in the German Clinical Trial Registry (DRKS00017253). The manuscript follows the STROBE guideline. The data supporting the findings of this study are available from the corresponding author on reasonable request from any qualified investigator.

Imaging biomarkers of cerebral atrophy and white matter lesions

Native CT scans from primary admission for stroke evaluation prior to acute stroke treatment were rated by trained neuroradiology physicians blinded from outcome parameters. Assessment included parameters of cerebral atrophy, namely global cortical atrophy score (GCA, ranging from 0 to 3 with 3 representing severe atrophy) (Pasquier et al., 1996), posterior atrophy score (PA, Koedam, ranging from 0 to 3 with 3 representing severe atrophy) (Koedam et al., 2011), and medial temporal lobe atrophy score (MTA, ranging from 0 to 4 with 4 representing end stage atrophy) (Scheltens et al., 1992). Burden of WML was assessed by Fazekas score (ranging from 0 to 3 with 3 representing the highest burden of WML) (Fazekas et al., 1987). Taking into account normative values of brain atrophy (Cotta

Ramusino et al., 2019; Rhodius-Meester et al., 2017), age-specific cut-offs for pathological score values were set as follows: pathological GCA <75 years: ≥1, ≥75 years: ≥2; pathological PA <65 years: ≥1, ≥65 years: ≥2; pathological MTA <65 years: ≥1, 65–79 years: >2, ≥80 years: ≥3; pathological Fazekas <65 years: ≥1, 65–74 years: ≥2, ≥75 years: 3.

Statistical analysis

The study cohort was divided into two comparison groups depending on diagnosis of delirium during hospital stay following MT. Statistical analyses were carried out on the basis of complete datasets for the respective outcome parameter. Data is presented as mean ± SD, median (interquartile range, IQR) or proportions (categorical variables), unless indicated otherwise. Number of available observations is stated for each variable. To identify patient-, stroke- and treatment characteristics associated with delirium, group comparison on univariate level was performed by Mann–Whitney-U test, chi-square test or Fishers exact test as appropriate. To investigate independent predictors of delirium and a potential predictive capacity of imaging parameters of neurodegeneration, a multiple logistic regression analysis was conducted. Variables were entered blockwise with demographic patient characteristics (age, sex) and variables significantly differing on univariate level in the first block, followed by a second block with stepwise variable selection by backward elimination containing scores on atrophy (GCA, Koedam, MTA), WML (Fazekas) and premorbid clinical diagnosis of dementia, to investigate a potential additional predictive power of these variables. Analysis of the area under the receiver operating characteristic (ROC) curve (AUC) was performed to assess predictive power of the regression model.

To assess predictive capacity of an existing screening instrument developed by Oldenbeuving et al. (2014) to identify acute stroke patients with high risk of delirium, we accordingly calculated their risk score 'Model 2' (containing age, National Institute of Health Stroke Scale [NIHSS] on admission, stroke subtype and presence of infection) and 'Model 3' (containing only age and NIHSS on admission) for patients in our cohort and conducted an AUC comparison between our multiple regression model and the proposed scoring system.

To assess an independent association of delirium with functional/cognitive outcome, multiple logistic regression analysis (functional outcome) and multiple linear regression analysis (cognitive outcome) was performed. The models adjust for the following confounders, selected by significant differences on univariate level and literature-based predictors of outcome following MT: age, sex, premorbid disability (mRS > 2), NIHSS on admission, intravenous thrombolysis, general anesthesia during MT, successful recanalization (thrombolysis in cerebral infarction scale score [TICI] 2b-3), time from admission to flow restoration, stroke etiology and pneumonia. Linearity was assessed using the Box-Tidwell procedure. All continuous variables were found to follow a linear relationship. For multicollinearity diagnostics, we calculated variance inflation factors, assuming no relevant multicollinearity for values <10. Predictive capacity of the multiple logistic regression models was assessed by Nagelkerke's R^2. Goodness of fit was assessed using the Hosmer-Lemeshow-Test, indicating a good model fit for $p > 0.05$. Multiple regression modelling was performed on the basis of complete datasets on the analyzed outcome and predictor variables. A significant difference was considered for $p < 0.05$ in all analyses. Statistical analyses were performed using SPSS (version 29, IBM, Armonk, NY, United States) and MedCalc Statistical Software (version 19.6, MedCalc Software Ltd., Ostend, Belgium).

Results

Univariate predictors of delirium following mechanical thrombectomy and associated outcome parameters

Baseline-, stroke- and treatment characteristics

Our analysis included 747 patients (median age 77.0 years, 53.4% female, Table 1). Of these, 8.2% ($n = 61$) were diagnosed with delirium during their hospital stay following MT of LVO. In univariate group comparison, patients with delirium were more often male (60.7% versus 45.3%, $p = 0.022$) and had more often relevant premorbid disability, measured by pre-stroke mRS > 2 (20.0% [12/60] versus 10.9% [71/673]; $p = 0.035$, Figure 1A). There was no significant difference in cardiovascular risk factor burden, nor did we note a significant difference in premorbid clinical diagnosis of dementia in patients with or without delirium (6.6% versus 4.1%, $p = 0.360$). Stroke severity, measured by NIHSS on admission (see also Figure 1B), and vessel territory of LVO were also similar. With regard to stroke etiology, we report more strokes classified as "other determined" etiology in patients with delirium (20.0% [12/60] versus 9.0% [59/656], $p = 0.006$). Treatment characteristics were similar between groups with regard to application of bridging intravenous thrombolysis, rates of referral for MT from another hospital, treatment times and rates of successful reperfusion, defined by TICI 2b-3. Rates of general anesthesia use during MT were much higher in patients developing delirium (50.9% [29/57] versus 30.8% [200/649], $p = 0.002$). Patients diagnosed with delirium more often had acute infectious complications (62.3% versus 42.7%, $p = 0.003$), encompassing pneumonia, urinary tract infection and/or sepsis. Especially pneumonia was more common in patients with delirium (50.8% versus 34.0%, $p = 0.008$).

Atrophy patterns and white matter lesions on native CT

The distribution of all three scoring systems on cerebral atrophy (GCA, Koedam, MTA) significantly differed between study groups (Figure 1C; Table 2). The proportion of patients exceeding age-specific cut-off values for cerebral atrophy was significantly higher in patients with delirium (GCA: 54.1% versus 38.5%. $p = 0.015$; Koedam: 31.1% versus 16.4%, $p = 0.004$; MTA: 24.6% versus 11.7%, $p = 0.004$). WML burden was similar with regard to distribution between groups as well as proportion of patients exceeding age-specific cut-offs.

Functional and cognitive outcome parameters

Patients with delirium had a longer duration of hospital stay and worse functional outcome at 90-day follow-up (Table 3). Good functional outcome was less frequent in patients with delirium (19.3% [11/57] versus 37.1% [226/609], $p = 0.007$, Figure 1D) as was excellent outcome. Mortality until 90-day follow-up was similar in both groups

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TABLE 1 Patient-, stroke- and treatment characteristics in patients with and without developing delirium following mechanical thrombectomy of large vessel occlusion ischemic stroke.

Variable	No delirium (*n* = 686)	Delirium (*n* = 61)	*p* value
Patient characteristics			
Age (years)	77 (65–83) (*n* = 686)	79 (69.5–84.5) (*n* = 61)	0.176
Male Sex	45.3% (311/686)	60.7% (37/61)	**0.022**
Premorbid disability (mRS 3–5)	10.9% (71/652)	20.0% (12/60)	**0.035**
History of dementia	4.1% (28/686)	6.6% (4/61)	0.360
Cardiovascular risk factors			
Arterial hypertension	78.3% (527/673)	80.0% (48/60)	0.760
Diabetes mellitus	27.5% (183/665)	32.2% (19/59)	0.442
Dyslipidemia	44.2% (293/663)	38.3% (23/60)	0.381
Atrial fibrillation	43.2% (288/667)	46.6% (27/58)	0.619
Smoker (current)	14.3% (80/559)	24.0% (12/50)	0.067
Stroke characteristics			
NIHSS on admission	14 (9–17) (*n* = 637)	14 (9–18) (*n* = 57)	0.485
Presenting with aphasia	45.6% (313/686)	42.6% (26/61)	0.652
Location of occlusion			
Carotid artery	21.2% (145/683)	21.3% (13/61)	0.988
Anterior cerebral artery	2.9% (20/683)	1.6% (1/61)	1.000
Middle cerebral artery M1 segment	52.6% (359/683)	44.3% (27/61)	0.214
Middle cerebral artery M2 segment	26.9% (184/683)	32.8% (20/61)	0.327
Posterior cerebral artery	3.1% (21/683)	3.3% (2/61)	0.712
Vertebrobasilar	11.4% (78/683)	14.8% (9/61)	0.438
Side of occlusion			0.681
Left	43.5% (297/682)	36.1% (22/61)	
Right	46.2% (315/682)	52.5% (32/61)	
Bilateral	0.3% (2/682)	0.0% (0/61)	
Not applicable (e.g., BA)	10.0% (68/682)	11.5% (7/61)	
Stroke etiology			
Large artery atherosclerosis	16.0% (105/656)	8.3% (12/60)	0.115
Cardioembolism	50.5% (331/656)	51.7% (31/60)	0.858
Dissection	1.8% (12/656)	3.3% (2/60)	0.331
Other determined	9.0% (59/656)	20.0% (12/60)	**0.006**
Undetermined	22.7% (149/656)	16.7% (10/60)	0.281
Treatment characteristics			
Intravenous thrombolysis	47.9% (325/679)	55.0% (33/60)	0.289
Primary admission at MT site	59.4% (401/675)	57.6% (34/59)	0.790
Symptom onset/Time of recognition-to-admission (minutes)	108.5 (60–190) (*n* = 594)	90 (60–205) (n = 53)	0.960
Door-to-groin puncture (minutes)	60 (31–87) (*n* = 616)	57.5 (28–95.25) (*n* = 54)	0.992
General anesthesia used	30.8% (200/649)	50.9% (29/57)	**0.002**
Successful reperfusion (TICI 2b-3)	81.4% (540/663)	88.1% (52/59)	0.200
Infectious complications			
Acute infection (total of below)	42.7% (293/686)	62.3% (38/61)	**0.003**
- Pneumonia	34.0% (233/686)	50.8% (31/61)	**0.008**

(Continued)

TABLE 1 (Continued)

Variable	No delirium (n = 686)	Delirium (n = 61)	p value
- Urinary tract infection	13.7% (94/686)	18.0% (11/61)	0.351
- Sepsis	3.1% (21/686)	3.3% (2/61)	0.711

Data are presented as percentage (absolute number) except for age, NIHSS on admission, symptom onset/time of recognition-to-admission, door-to-groin puncture: median (IQR) (number of available observations). mRS: modified Rankin Scale; MT: mechanical thrombectomy; NIHSS: National Institutes of Health Stroke Scale; TICI: Thrombolysis in cerebral infarction scale.

(31.6% [18/57] versus 34.5% [210/609], $p = 0.659$). With regard to cognitive outcome, measured by MoCA at 90-day follow-up, we report no significant difference between groups (median [IQR]: 16 [11–21] versus 19 [16–20], $p = 0.212$, Figure 1E).

Independent predictors of delirium following mechanical thrombectomy

Resulting from multiple logistic regression modelling, independent predictors of delirium were older age (aOR[95%CI] per year: 1.034[1.005–1.065], $p = 0.023$), male sex (aOR[95%CI]: 2.173[1.182–3.994], $p = 0.012$), general anesthesia during MT (aOR[95%CI]: 2.455[1.385–4.352], $p = 0.002$), infectious complications (aOR[95%CI]: 1.845[1.031–3.305], $p = 0.039$), and "other determined" etiology of stroke (aOR[95%CI]: 2.424[1.100–5.345], $p = 0.028$). Regarding atrophy scores (GCA, Koedam, MTA), Fazekas score and pre-existing clinical diagnosis of dementia, only MTA exceeding age-specific cut-offs emerged from the model as an independent predictor of delirium (aOR[95%CI]: 2.126[1.065–4.244], $p = 0.033$, see also Figure 1F). For detailed model characteristics, see also Table 4.

Predictive capacity of multiple regression model and comparison with published scoring system for delirium prediction in stroke patients

In ROC analysis, the multiple regression model yielded significant predictive capacity with an AUC [95%CI] of 0.725[0.690–0.759] ($p < 0.001$, Figure 1G). Applying the proposed scoring instrument of Oldenbeuving et al. (2014) to our dataset, we report an AUC [95%CI] of 0.611[0.573–0.648] for their 'model2' (containing age, NIHSS on admission, stroke subtype and presence of infection) in our cohort of patients with LVO treated by MT. Their simplified score 'model3' (containing only age and NIHSS on admission) resulted in an AUC [95%CI] of 0.588[0.549–0.625]. Thus, both models performed significantly worse than our multiple regression model in prediction of delirium following MT of LVO ($p = 0.005$ for 'model2', $p = 0.006$ for 'model 3').

Independent association of delirium with worse functional outcome

Adjusting for differences between study groups and literature-based predictors of outcome after MT of LVO, we report an independent association of delirium with worse functional outcome. Patients with delirium were less likely to achieve good functional outcome (aOR[95%CI]: 2.902[1.005–8.383], $p = 0.049$) or excellent functional outcome (aOR[95%CI]: 3.440[1.045–11.327], $p = 0.042$). We did not observe an independent association of delirium with mortality or cognitive outcome. For details, see Table 4.

Discussion

We here show that delirium is a complication associated with worse functional outcome in patients with LVO who were treated by MT and present data on conventional and novel predictive factors for development of delirium in these patients, which help to identify patients at risk and implement specific preventive measures to improve clinical outcome.

With regard to functional outcome, our results are in line with previous analyses of delirium in patients with acute stroke. These reported worse functional outcome in mixed stroke cohorts, mostly focusing on mortality and functional dependence at hospital dicharge (Shi et al., 2012; Rollo et al., 2022; Pasińska et al., 2019). Patients with LVO treated by MT were largely underrepresented in former studies of delirium in acute stroke and yet, depict a relevant share of the disease. We expand former findings by showing that also in stroke patients with LVO treated by MT delirium is associated with worse functional outcome at discharge. This finding persists three months after stroke and, notably, is independent of stroke severity. We consider this remarkable, especially since functional outcome in patients with major ischemic stroke due to LVO is mainly driven by severity of the disease. In contrast to former studies of delirium in stroke patients, we did not observe increased mortality in patients with LVO who developed delirium, which is likely due to high overall mortality rates attributable to other complications and severity of the disease. Increased hospital stay duration has been reported in patients with delirium in mixed stroke cohorts (Shi et al., 2012). This was also true for our patients treated by MT. This is notable, because in this cohort, hospital discharge is often determined by stroke-associated neurological deficits affecting independence in daily activities and self-care.

Our analyses identify patient-, stroke- and treatment characteristics that are associated with development of delirium in patients treated by MT. These have direct clinical implications by enabling identification of patients at risk for delirium to target preventive measures or contribute to early diagnosis. As expected, older age and infectious complications were independently associated with delirium following MT. These are known risk factors for delirium in hospitalized patients and, as shown previously, in patients with acute stroke (Oldenbeuving et al., 2011). We observed male sex to be independently associated with development of delirium following MT. This is especially interesting and merits further investigation, since prospective validated prediction models do not describe sex as a risk factor for delirium (Inouye et al., 2014; Zaal et al., 2015). Potentially, a difference in motor subtypes of delirium could contribute

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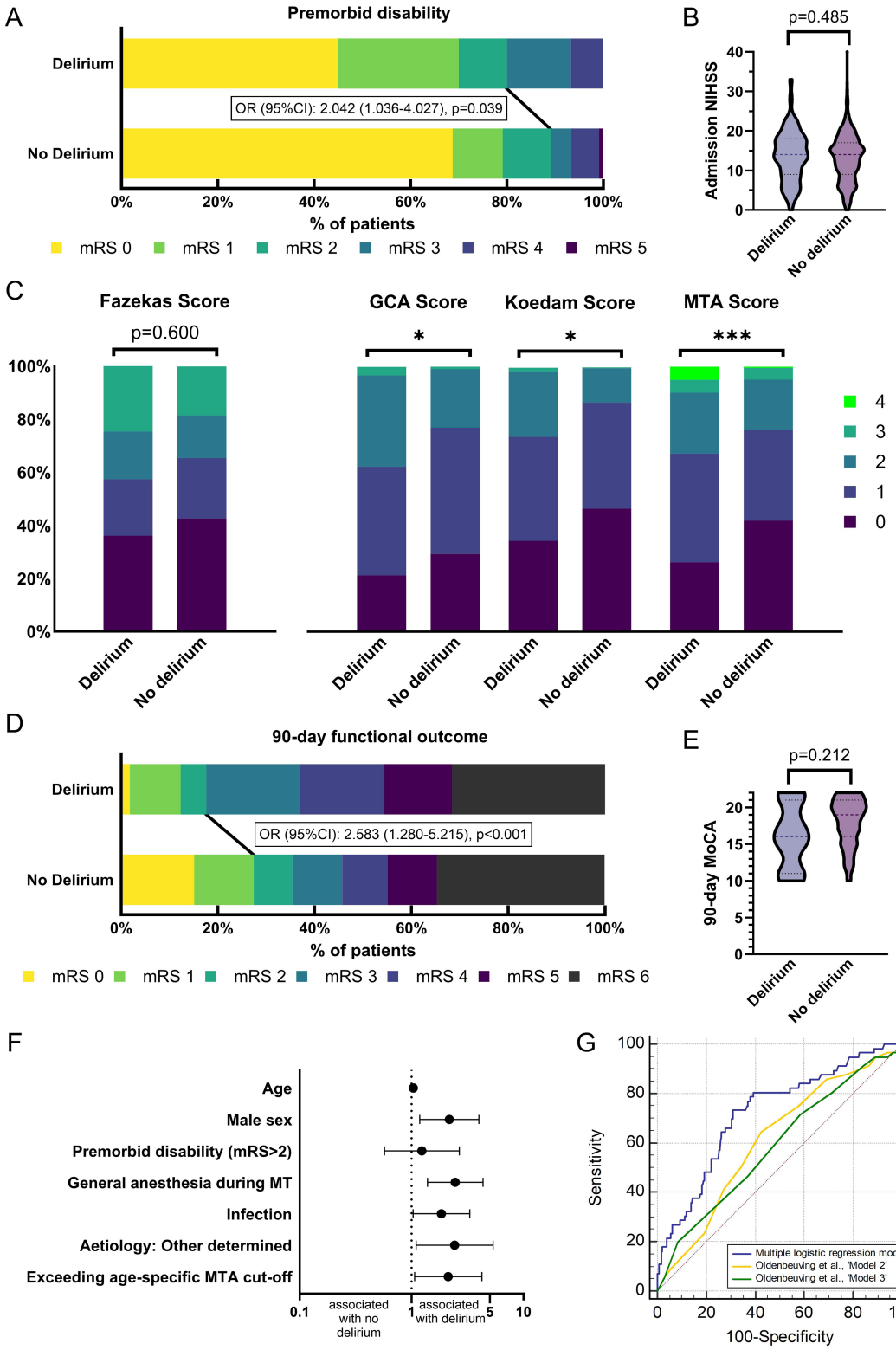

FIGURE 1
Outcomes and determinants of delirium in patients treated by mechanical thrombectomy. **(A)** Distribution of premorbid mRS in patients with and without delirium. Patients with delirium have significantly higher premorbid disability. **(B)** No significant differences in stroke severity measured by NIHSS on admission in patients with and without delirium. **(C)** White matter lesion burden (Fazekas) does not differ between patients with and without delirium. Distribution of all cerebral atrophy scores (GCA, Koedam, MTA) is significantly different in patients with versus without delirium. **(D)** Distribution of mRS at 90-day follow-up in patients with and without delirium. Patients with delirium have significantly worse functional outcome. **(E)** No significant differences in cognitive outcome (MoCA) at 90-day follow-up in patients with and without delirium. **(F)** Independent predictors of delirium following MT of LVO. Displayed are odds ratios with 95%CI resulting from multiple logistic regression analysis. **(G)** AUC analysis of multiple

(Continued)

FIGURE 1 (Continued)
logistic regression model yields significant predictive capacity of delirium following MT of LVO. In AUC comparison, predictive capacity is significantly higher than with previously developed tools for risk stratification for delirium in stroke patients by Oldenbeuving et al. (2014). Asterisks: *p*-values indicating significant difference under a threshold of *: <0.05; ***: <0.001. AUC: Area under the receiver operating characteristic curve, GCA: global cortical atrophy score, Koedam: posterior atrophy score, LVO: large vessel occlusion, MoCA: Montreal Cognitive Assessment, MT: mechanical thrombectomy, MTA: medial temporal lobe atrophy score, NIHSS: National Institute of Health Stroke Scale, IVT: intravenous thrombolysis, mRS: modified Rankin Scale score.

TABLE 2 Atrophy patterns and white matter lesions in patients with and without delirium.

Variable	No delirium (*n* = 686)	Delirium (*n* = 61)	*p* value
Global cortical atrophy score (GCA)			
- Absent	29.3% (200/683)	21.3% (13/61)	**0.037**
- Grade 1	47.7% (326/683)	41.0% (25/61)	
- Grade 2	22.1% (151/683)	34.4% (21/61)	
- Grade 3	0.9% (6/683)	3.3% (2/61)	
- Exceeding age-specific cut-off	38.5% (263/683)	54.1% (33/61)	**0.015**
Posterior atrophy score (Koedam)			
- Absent	46.4% (317/683)	34.4% (21/338)	**0.032**
- Grade 1	40.1% (274/683)	39.3% (24/61)	
- Grade 2	13.0% (89/683)	24.6% (15/61)	
- Grade 3	0.4% (3/683)	1.6% (1/61)	
- Exceeding age-specific cut-off	16.4% (112/683)	31.1% (19/61)	**0.004**
Medial temporal lobe atrophy score (MTA)			
- Absent	41.9% (286/683)	26.5% (16/61)	**<0.001**
- Grade 1	34.3% (234/683)	41.0% (25/61)	
- Grade 2	19.0% (130/683)	23.0% (14/61)	
- Grade 3	4.4% (30/683)	4.9% (3/61)	
- Grade 4	0.4% (3/683)	4.9% (3/61)	
- Exceeding age-specific cut-off	11.7% (80/683)	24.6% (15/61)	**0.004**
White matter lesions (Fazekas score)			
- Absent	42.6% (291/683)	36.1% (22/61)	0.600
- Grade 1	22.8% (156/683)	21.3% (13/61)	
- Grade 2	16.1% (110/683)	18.0% (11/61)	
- Grade 3	18.4% (126/683)	24.6% (15/61)	
- Exceeding age-specific cut-off	23.9% (163/683)	27.9% (17/61)	0.484

Data are presented as percentage (absolute number).

TABLE 3 Outcome parameters in patients with and without developing delirium following mechanical thrombectomy of large vessel occlusion ischemic stroke.

Outcome parameter	No delirium (*n* = 686)	Delirium (*n* = 61)	*p* value
Duration of hospital stay (days)	9 (5–13) (*n* = 679)	13 (7.25–17) (*n* = 60)	**<0.001**
Excellent outcome at 90-day follow-up (mRS ≤1 or as pre-mRS)	29.4% (179/609)	14.0% (8/57)	**0.014**
Good outcome at 90-day follow-up (mRS ≤2 or as pre-mRS)	37.1% (226/609)	19.3% (11/57)	**0.007**
90-day mortality	34.5% (210/609)	31.6% (18/57)	0.659
MoCA at 90-day follow-up	19 (16–20) (*n* = 210)	16 (11–21) (*n* = 11)	0.212

Data are presented as percentage (absolute number) except for duration of hospital stay, MoCA: median (IQR) (number of available observations). mRS: modified Rankin Scale; MoCA: Montreal Cognitive Assessment.

to our observation. Supporting this, a recent meta-analysis reports that hypoactive cases of delirium were more likely to be female (Ghezzi et al., 2022). Consequently, this might lead to increased diagnosis of delirium in men in observational routine care data, especially since persisting neurological deficits further impede diagnosis of delirium following MT of LVO (Vater et al., 2024).

TABLE 4 Independent predictors of delirium and independent association of delirium with functional and cognitive outcome at 90-day follow-up.

Independent predictors of delirium resulting from multiple logistic regression modelling Model characteristics: Nagelkerkes R^2 = 0.127, $p < 0.001$			
Variable	Adjusted odds ratio	95% CI	*p*-value
Age	1.034	1.005–1.065	**0.023**
Male sex	2.173	1.182–3.994	**0.013**
Premorbid disability (mRS 3–5)	1.236	0.572–2.674	0.590
General anesthesia during MT	2.455	1.385–4.352	**0.002**
Infectious complication	1.845	1.031–3.305	**0.039**
Etiology: "other determined"	2.424	1.100–5.345	**0.028**
Exceeding age-specific MTA cut-off	2.126	1.065–4.244	**0.033**

Independent association of delirium with functional and cognitive outcome at 90-day follow-up			
Variable	Adjusted odds ratio/β-coefficient	95% CI	*p*-value
Not achieving excellent outcome at 90-day follow-up (mRS ≤ 1 or as premorbid mRS)	3.440	1.045–11.327	**0.042**
Not achieving good outcome at 90-day follow-up (mRS ≤ 2 or as premorbid mRS)	2.902	1.005–8.383	**0.049**
90-day mortality	0.773	0.321–1.859	0.565
MoCA at 90-day follow-up	−0.242	−2.557-2.074	0.837

Point estimates, 95% CI and corresponding *p*-values resulting from multiple logistic/linear regression modelling. The multiple regression models assessing independent association of delirium with functional/cognitive outcome adjust for the following confounders: age, sex, premorbid disability (mRS > 2), NIHSS on admission, intravenous thrombolysis, general anesthesia during MT, successful recanalization (thrombolysis in cerebral infarction scale score [TICI] 2b-3), time from admission to flow restoration, stroke etiology and pneumonia. mRS: modified Rankin Scale; MT: mechanical thrombectomy; MTA: Medial temporal lobe atrophy score; MoCA: Montreal Cognitive Assessment.

Premorbid cognitive decline and cerebral atrophy have been repeatedly reported to be associated with development of delirium in patients with acute stroke. Investigation of the predictive capacity of cerebral atrophy for delirium in these patients, independent of conventional risk factors, has yielded conflicting results (Oldenbeuving et al., 2011; Rhee et al., 2022; Czyzycki et al., 2021; Qu et al., 2018). We show that a pathologic MTA score may be an easily accessible biomarker in native CT imaging that is independently associated with a 2-fold increase of odds for development of delirium following MT. Pathological MTA scores are associated with cognitive decline and Alzheimer's disease (Scheltens et al., 1992). However and interestingly, premorbid clinical diagnosis of dementia was neither more frequent in patients with delirium nor adding predictive value to multiple regression modelling of delirium in our cohort. Increased awareness among stroke-unit personnel for the need of delirium prevention in patients with known dementia and consecutively better preventive measures may have potentially contributed to absence of increased delirium rates in these patients. However, it is more likely that this observation may be due to underdiagnosis of dementia or early phases of cognitive decline, not yet diagnosed as dementia, but apparent as brain atrophy. Similarly, underreporting of dementia diagnosis when obtaining medical history from a third party, as is often the case for patients with major ischemic stroke treated by MT, may contribute to our observation. Consequentially, pathological MTA scores, as an objective CT imaging biomarker associated with cognitive decline may provide additional predictive benefit instead.

With regard to treatment characteristics, the use of general anesthesia during MT was the only procedural feature independently associated with development of delirium. We report an almost 2.5-fold increase of odds to develop delirium following MT under general anesthesia. This finding is new in patients with LVO treated by MT and is clearly supported by systemic reviews reporting strong evidence for mechanical ventilation as a precipitating factor for delirium in the intensive care unit (Zaal et al., 2015). The role of anesthesia type during MT in functional outcome is controversially discussed (Sarraj et al., 2023; Chabanne et al., 2023; Campbell et al., 2023). Although further investigation is warranted, our finding demonstrates that delirium is a potential complication associated with use of general anesthesia during MT and argues against its across-the-board use in the management of LVO MT. Future studies should examine, whether patients developing delirium after MT benefit less from general anesthesia during MT, and, whether risk stratification for benefit of general anesthesia during MT could be improved by including independent risk factors for developing delirium.

Only few predictive tools exist to identify individuals with acute stroke at high risk of developing delirium (Drozdowska et al., 2021). Even though internal validation of these tools yielded comparatively high predictive capacity within the small mixed stroke cohorts they were derived from, it is questionable whether such tools are applicable to patients with LVO treated by MT. Such developed tools only provided limited predictive power in our cohort of MT-treated patients. We suggest that this is partly due to high weights placed on stroke severity in published predictive tools. This appears to enable identification of individuals at risk in mixed stroke cohorts, yet might be of limited significance in cohorts of patients with major stroke due to LVO. In line with this, we observed no significant difference in NIHSS on admission in patients with

and without delirium in our cohort. Additional factors associated with delirium in MT-treated patients may enhance risk stratification in this distinct subgroup of acute stroke patients and should be considered in risk assessment for developing delirium in these patients.

Despite analyzing a broad dataset of patient-, stroke- and treatment characteristics, our study approach has several limitations. We observed a comparatively low incidence of delirium (8.2%) in our study cohort. The literature is inconsistent with a broad range regarding delirium incidence following acute stroke, yet observational data from routine care, as is our dataset, might be prone to underdiagnosis of delirium. Especially hypoactive phenotypes of the disease might be underdiagnosed. The implementation of screening for delirium on a regular basis, as has recently been added to national guidelines of acute stroke care (Ringleb et al., 2022), might help to overcome this potential source of bias in the future and allow for even more accurate analyses of delirium from observational data. Furthermore, reduced sensitivity for diagnosis of delirium has been shown for ICD-10 diagnoses, e.g., compared to discharge reports (Chuen et al., 2022; Thomas et al., 2012), which might further explain the comparatively low delirium incidence in our dataset. Due to the nature of our monocentric study cohort, our findings are also limited with regard to transferability and generalizability. Our analysis might also have limited generalizability to populations with an ethnical distribution differing from the western European one. Future studies should confirm and further examine our findings.

Our analysis is based on a well-characterized large cohort of patients with major stroke due to LVO treated by MT. Therefore, we were able to investigate a comprehensive set of stroke- and treatment characteristics, potentially associated with delirium. As delirium has previously only been analyzed in mixed stroke cohorts with few cases treated by MT, our findings are new and highly relevant for acute care of these patients. Furthermore, we identify risk factors and an imaging biomarker in native CT that are easy to obtain in clinical practice. This is an important advantage with regard to transferability into clinical practice for identification of individuals at high risk of developing delirium following MT.

Conclusion

We demonstrate that previously developed tools for identifying stroke patients at high risk for delirium have only limited predictive capacity in a cohort of patients treated by MT. Besides conventional risk factors such as age and infectious complications, additional risk factors for delirium exist that were not included in tools for risk stratification in mixed stroke cohorts until now. A pathologic MTA score, rated in native CT, may be an easy to use imaging biomarker identifying patients at increased risk for delirium following MT as is the use of general anesthesia during the MT procedure. Prevention of delirium is our best therapeutic strategy, as therapy options, once incident, are limited. Identification of individuals at high risk may help to intensify preventive measures and allow for a targeted resource allocation. The fact that delirium is associated with worse functional outcome, even in our cohort of severely diseased patients with LVO, justify and stress the importance of increased efforts to predict and prevent this complication.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Ethics statement

The studies involving humans were approved by Ethics committee of the Landesärztekammer Rheinland-Pfalz (approval number: 2018-13335-Epidemiologie). The studies were conducted in accordance with the local legislation and institutional requirements. The participants or guardians of participants provided their written informed consent to participate in this study.

Author contributions

MH: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Visualization, Writing – original draft. LB: Data curation, Methodology, Investigation Writing – review & editing. SG: Writing – review & editing. KaG: Writing – review & editing. NG: Writing – review & editing. MB: Writing – review & editing. AO: Writing – review & editing. KlG: Investigation, Supervision, Writing – review & editing. TU: Data curation, Investigation, Methodology, Supervision, Writing – review & editing.

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Conflict of interest

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The remaining authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fnagi.2025.1486726/full#supplementary-material

References

Burton, J. K., Craig, L. E., Yong, S. Q., Siddiqi, N., Teale, E. A., Woodhouse, R., et al. (2021). Non-pharmacological interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database Syst. Rev.* 7:CD013307. doi: 10.1002/14651858.CD013307.pub2

Campbell, D., Butler, E., Campbell, R. B., Ho, J., and Barber, P. A. (2023). General anesthesia compared with non-GA in endovascular Thrombectomy for ischemic stroke: a systematic review and Meta-analysis of randomized controlled trials. *Neurology* 100, e1655–e 1663. doi: 10.1212/WNL.0000000000207066

Chabanne, R., Geeraerts, T., Begard, M., Balança, B., Rapido, F., Degos, V., et al. (2023). Outcomes after endovascular therapy with procedural sedation vs general anesthesia in patients with acute ischemic stroke: the AMETIS randomized clinical trial. *JAMA Neurol.* 80, 474–483. doi: 10.1001/jamaneurol.2023.0413

Chuen, V. L., Chan, A. C. H., Ma, J., Alibhai, S. M. H., and Chau, V. (2022). Assessing the accuracy of international classification of diseases (ICD) coding for delirium. *J. Appl. Gerontol.* 41, 1485–1490. doi: 10.1177/07334648211067526

Cotta Ramusino, M., Altomare, D., Bacchin, R., Ingala, S., Bnà, C., Bonetti, M., et al. (2019). Medial temporal lobe atrophy and posterior atrophy scales normative values. *Neuroimage Clin.* 24:101936. doi: 10.1016/j.nicl.2019.101936

Czyzycki, M., Glen, A., Slowik, A., Chrzan, R., and Dziedzic, T. (2021). Clinical utility of brain computed tomography in prediction of post-stroke delirium. *J. Neural. Transm. (Vienna)* 128, 207–213. doi: 10.1007/s00702-020-02294-9

Drozdowska, B. A., McGill, K., McKay, M., Bartlam, R., Langhorne, P., and Quinn, T. J. (2021). Prognostic rules for predicting cognitive syndromes following stroke: a systematic review. *Eur. Stroke J.* 6, 18–27. doi: 10.1177/2396987321997045

Fazekas, F., Chawluk, J. B., Alavi, A., Hurtig, H. I., and Zimmerman, R. A. (1987). MR signal abnormalities at 1.5 T in Alzheimer's dementia and normal aging. *AJR Am. J. Roentgenol.* 149, 351–356. doi: 10.2214/ajr.149.2.351

Ghezzi, E. S., Greaves, D., Boord, M. S., Davis, D., Knayfati, S., Astley, J. M., et al. (2022). How do predisposing factors differ between delirium motor subtypes? A systematic review and meta-analysis. *Age Ageing* 51, 1–13. doi: 10.1093/ageing/afac200

Hahn, M., Gröschel, S., Gröschel, K., and Uphaus, T. (2023). Association of Delirium Incidence with visitation restrictions due to COVID-19 pandemic in patients with acute cerebrovascular disease in a stroke-unit setting: a retrospective cohort study. *Gerontology* 69, 273–281. doi: 10.1159/000526165

Inouye, S. K., Westendorp, R. G. J., and Saczynski, J. S. (2014). Delirium in elderly people. *Lancet* 383, 911–922. doi: 10.1016/S0140-6736(13)60688-1

Koedam, E. L. G. E., Lehmann, M., van der Flier, W. M., Scheltens, P., Pijnenburg, Y. A. L., Fox, N., et al. (2011). Visual assessment of posterior atrophy development of a MRI rating scale. *Eur. Radiol.* 21, 2618–2625. doi: 10.1007/s00330-011-2205-4

Lütz, A., Radtke, F. M., Franck, M., Seeling, M., Gaudreau, J.-D., Kleinwächter, R., et al. (2008). Die Nursing Delirium Screening Scale (Nu-DESC)—Richtlinienkonforme Ubersetzung für den deutschsprachigen Raum. *Anasthesiol. Intensivmed. Notfallmed. Schmerzther.* 43, 98–102. doi: 10.1055/s-2008-1060551

Nasreddine, Z. S., Phillips, N. A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., et al. (2005). The Montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.* 53, 695–699. doi: 10.1111/j.1532-5415.2005.53221.x

Oldenbeuving, A. W., Kort, P. L. M., Jansen, B. P. W., Algra, A., Kappelle, L. J., and Roks, G. (2011). Delirium in the acute phase after stroke: incidence, risk factors, and outcome. *Neurology* 76, 993–999. doi: 10.1212/WNL.0b013e318210411f

Oldenbeuving, A. W., Kort, P. L. M., van Eck Sluijs, J. F., Kappelle, L. J., and Roks, G. (2014). An early prediction of delirium in the acute phase after stroke. *J. Neurol. Neurosurg. Psychiatry* 85, 431–434. doi: 10.1136/jnnp-2013-304920

Pasińska, P., Wilk, A., Kowalska, K., Szyper-Maciejowska, A., and Klimkowicz-Mrowiec, A. (2019). The long-term prognosis of patients with delirium in the acute phase of stroke: PRospective observational POLIsh study (PROPOLIS). *J. Neurol.* 266, 2710–2717. doi: 10.1007/s00415-019-09471-1

Pasquier, F., Leys, D., Weerts, J. G., Mounier-Vehier, F., Barkhof, F., and Scheltens, P. (1996). Inter-and intraobserver reproducibility of cerebral atrophy assessment on MRI scans with hemispheric infarcts. *Eur. Neurol.* 36, 268–272. doi: 10.1159/000117270

Qu, J., Chen, Y., Luo, G., Zhong, H., Xiao, W., and Yin, H. (2018). Delirium in the acute phase of ischemic stroke: incidence, risk factors, and effects on functional outcome. *J. Stroke Cerebrovasc. Dis.* 27, 2641–2647. doi: 10.1016/j.jstrokecerebrovasdis.2018.05.034

Rhee, J. Y., Colman, M. A., Mendu, M., Shah, S. J., Fox, M. D., Rost, N. S., et al. (2022). Associations between stroke localization and delirium: a systematic review and Meta-analysis. *J. Stroke Cerebrovasc. Dis.* 31:106270. doi: 10.1016/j.jstrokecerebrovasdis.2021.106270

Rhodius-Meester, H. F. M., Benedictus, M. R., Wattjes, M. P., Barkhof, F., Scheltens, P., Muller, M., et al. (2017). MRI visual ratings of brain atrophy and white matter Hyperintensities across the Spectrum of cognitive decline are differently affected by age and diagnosis. *Front. Aging Neurosci.* 9:117. doi: 10.3389/fnagi.2017.00117

Ringleb, P., Köhrmann, M., Jansen, O., Berlis, A., Fischer, U., Laufs, U., et al. Akuttherapie des ischämischen Schlaganfalls, S2e-Leitlinie. Leitlinien für Diagnostik und Therapie in der Neurologie. (2022) [cited 2023 Sep 26]. Available at: www.dgn.org/leitlinien

Rollo, E., Brunetti, V., Scala, I., Callea, A., Marotta, J., Vollono, C., et al. (2022). Impact of delirium on the outcome of stroke: a prospective, observational, cohort study. *J. Neurol.* 269, 6467–6475. doi: 10.1007/s00415-022-11309-2

Sarraj, A., Albers, G. W., Mitchell, P. J., Hassan, A. E., Abraham, M. G., Blackburn, S., et al. (2023). Thrombectomy outcomes with general vs nongeneral anesthesia: a pooled patient-level analysis from the EXTEND-IA trials and SELECT study. *Neurology* 100, e336–e347. doi: 10.1212/WNL.0000000000201384

Scheltens, P., Leys, D., Barkhof, F., Huglo, D., Weinstein, H. C., Vermersch, P., et al. (1992). Atrophy of medial temporal lobes on MRI in "probable" Alzheimer's disease and normal ageing: diagnostic value and neuropsychological correlates. *J. Neurol. Neurosurg. Psychiatry* 55, 967–972. doi: 10.1136/jnnp.55.10.967

Shaw, R. C., Walker, G., Elliott, E., and Quinn, T. J. (2019). Occurrence rate of delirium in acute stroke settings: systematic review and Meta-analysis. *Stroke* 50, 3028–3036. doi: 10.1161/STROKEAHA.119.025015

Shi, Q., Presutti, R., Selchen, D., and Saposnik, G. (2012). Delirium in acute stroke: a systematic review and meta-analysis. *Stroke* 43, 645–649. doi: 10.1161/STROKEAHA.111.643726

Thomas, C., Kreisel, S. H., Oster, P., Driessen, M., Arolt, V., and Inouye, S. K. (2012). Diagnosing delirium in older hospitalized adults with dementia: adapting the confusion assessment method to international classification of diseases, tenth revision, diagnostic criteria. *J. Am. Geriatr. Soc.* 60, 1471–1477. doi: 10.1111/j.1532-5415.2012.04066.x

Vater, V., Olm, H.-P., and Nydahl, P. (2024). Delir bei Schlaganfall: systematisches Review und Metaanalyse. *Med Klin Intensivmed Notfmed* 119, 49–55. doi: 10.1007/s00063-023-01013-y

Zaal, I. J., Devlin, J. W., Peelen, L. M., and Slooter, A. J. C. (2015). A systematic review of risk factors for delirium in the ICU. *Crit. Care Med.* 43, 40–47. doi: 10.1097/CCM.0000000000000625

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