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Effectiveness of a Virtual Reality-Based Sensory Stimulation Intervention in Preventing Delirium in Intensive Care Units: A Randomized Controlled Trial Protocol

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ABSTRACT

Introduction:

This is the first randomized controlled trial (RCT) designed to evaluate the effects of a Virtual Reality-based sensory stimulation intervention on preventing delirium in intensive care unit (ICU) patients.

Methods and Analysis:

We employed a paired randomization method to match eligible participants based on a validated delirium risk scoring model for ICU patients. A consecutive sample of 324 ICU patients admitted to the study setting will be recruited. Eligible participants will be randomly allocated to receive either Virtual Reality-based sensory stimulation in addition to usual care or usual care alone. The Virtual Reality-based sensory stimulation intervention will last for up to fourteen days, with all interventions administered by a research team. The primary outcomes will include delirium incidence, duration, and severity. The secondary outcomes will encompass patients' psychological well-being (post-traumatic stress disorder, sleep quality, and ICU memory), patients' clinical outcomes, and other outcomes (quality of life, independence, and cognitive function). Data will be collected at baseline, post-intervention, and six months post-intervention. Paired-sample t-tests or paired Wilcoxon signed-rank tests, Kappa consistency tests, or McNemar's tests will be used for categorical variables. The study will adhere to the intention-to-treat principle for analysis. Mixed-effects models will be used to analyze differences between groups in delirium duration, delirium severity, psychological outcomes, and other outcomes.

Discussion:

The results will provide valuable information for stakeholders considering the integration of Virtual Reality-based sensory stimulation into routine nursing practice.

Ethics and dissemination This protocol was approved by Research Ethics Committee of Shenzhen Hospital of Southern Medical University (NYSZYYEC20230068). All participants will provide written informed consent. Results will be disseminated through scientific publications, and presentations at local and international conferences.

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Keywords: Critical care; Delirium, Virtual Reality, Sensory stimulation

Article Summary

Strengths and limitations of this study

► This study evaluates a Virtual Reality-based sensory stimulation for preventing delirium and improving patients' psychological well-being (specifically post-traumatic stress disorder, sleep quality, and ICU memory), patients' clinical outcomes (including ICU length of stay), and other outcomes (such as quality of life, independence, and cognitive function).

►To the best of the authors' knowledge, this is the first initiative to incorporate a Virtual Reality-based sensory stimulation intervention for preventing delirium in ICUs.

►Due to the nature of the intervention, blinding was only possible for the outcome assessors, while blinding for the participants and those delivering the intervention was not feasible.

INTRODUCTION

Delirium is a common acute state of cognitive confusion. Intensive Care Unit (ICU) delirium is highly prevalent, with an incidence ranging from 31%(1) to 56%(2), and it can be as high as 81%(3) in ICU patients undergoing mechanical ventilation. A preliminary analysis of data from 375 patients admitted to the ICU for more than 24 hours revealed an occurrence rate of 44% for ICU delirium(4). Moreover, delirious ICU patients had 1.33 times longer ICU stays and a 9.57-fold increase in mortality compared to non-delirious ICU patients(5). ICU patients who experience delirium may suffer from post-traumatic stress disorder, anxiety, depression, and cognitive impairment for up to two years(6).

Non-pharmacological preventive measures aim to reduce one or more modifiable risk factors for ICU delirium(7). Previous research identified sensory stimulation as a key and effective non-pharmacological intervention in preventing ICU delirium(8,9). Sensory stimulation involves activating one or more senses(10), with visual and auditory stimuli being particularly effective for ICU patients(11). To further investigate the effectiveness of sensory stimulation in preventing ICU delirium, the research team conducted an initial study to assess the implementation of sensory stimulation on preventing delirium in ICU and subsequently developed a sensory stimulation intervention plan(12,13). This plan involved daily sessions of 30 minutes each for seven days, including visual stimuli (displaying personal or family photos) and auditory stimuli (playing recordings of family members). The results of the study showed that sensory stimulation reduced the duration and severity of ICU delirium but did not significantly decrease the incidence of ICU delirium(8,9). The limited effectiveness of sensory stimulation may be attributed to the narrow range of stimuli, insufficient stimulus intensity, and inadequate dosing and implementation methods(9).

In contrast, Virtual Reality (VR) technology, characterized by its three-dimensional and highly immersive qualities, has the potential to provide more effective sensory stimulation by immersing participants in three-dimensional dynamic environments(14). International research conducted internationally suggests that VR offers significant advantages in sensory stimulation and could be a promising approach for preventing ICU delirium. However, it's important to note that studies on the use of VR in preventing ICU delirium are currently in the feasibility testing stage(15–17). The DREAMS project at the University of Florida in the United States investigated the effectiveness of VR and found that 95.6% of participants found it very comfortable, 51.9% reported improved sleep quality, and 81.5% experienced reduced pain(16). This team further conducted a study with 46 ICU patients, implementing a seven-day VR intervention, which resulted in reduced stress, pain, anxiety, and improved cognitive function and attention in the participants(17). Additionally, Jawed and colleagues conducted a preliminary trial that showed VR could alleviate anxiety in ICU patients(15). However, since those studies were in the feasibility testing stage, they were unable to measure the effects on reducing ICU delirium.

The stress recovery theory and attention restoration theory explain the principles behind preventing ICU delirium using VR-based sensory stimulation(18,19). The stress recovery theory suggests that natural environments support positive changes in emotional states and psychophysiological recovery, primarily by relaxing the parasympathetic nervous system (19). In stressful ICU environments, cognitive and attentional resources can become fatigued, which is especially crucial for critically ill patients facing stressors. The cognitive demands and overstimulation in the ICU environment contribute to mental fatigue and stress responses. On the other hand, the attention restoration theory suggests that exposure to natural environments

requires fewer cognitive resources and promotes a sense of disengagement from stressors, allowing attention to rest and recover(18). Therefore, VR-based visual and auditory stimuli, by immersing patients in relaxing VR environments, can have a protective effect against environmental stress and aid in the recovery of physiological, emotional, and attentional functions, thus preventing delirium. Chirico and colleagues further elucidated the mechanisms of VR-based sensory stimulation in delirium prevention: exposure to VR-based natural environments can trigger a specific psychophysiological pattern activated by the parasympathetic nervous system, leading to intense emotional reactions. Emotion responses increase with higher levels of immersion, which can be utilized to alleviate symptoms like anxiety, pain, and fear, effectively reducing patient stress, improving sleep quality, and consequently reducing the incidence of delirium(20).

Aim and hypothesis

This study aims to evaluate the effects of evaluates a Virtual Reality-based sensory stimulation on preventing delirium and improving patients' psychological (post-traumatic stress disorder, sleep quality, ICU memory), patients' clinical (ICU length of stay) and other outcomes (quality of life, independence and cognitive function). It is hypothesised that at patients' fourteenth day of ICU hospitalisation or the day of discharge (if the ICU stay is less than 14 days), will experience the following improvements compared with those receiving usual care.

1. ICU patients receiving the sensory stimulation intervention will have:
    a. A greater reduction in incidence, duration and severity of delirium.
    b. A significant improvement in their post-traumatic stress disorder.
    c. A significant improvement of factual memories.
    d. A shorter length of ICU stay.

e. A significant improvement in quality of life, independence and cognitive function.

At six months after completing the intervention, compared to those receiving usual care, ICU patients undergoing the VR-based sensory stimulation intervention will experience a significant improvement in quality of life, independence, and cognitive function.

METHODS AND ANALYSIS

Design

An assessor-blinded two-arm RCT will be conducted. Figure 1 shows the study flow.

Setting

Participants will be recruited from general ICUs of two comprehensive tertiary A -level hospitals in Shenzhen, Guangdong province, Mainland China. Tertiary A-level hospital provides specialist tertiary care in a large hospital after a referral from primary and secondary care.(21)

Participants

All ICU patients admitted to the study setting will be recruited if they are/have: (1) aged 18 years or older, (2) first-time admission to the ICU, and (3) a Richmond Agitation-Sedation Scale (RASS) score of ≥-3(22) . Patients will be excluded if they have: (1) been diagnosed with dementia, delirium or acute psychiatric illness at admission, (2) been diagnosed with end-stage cancer, (3) severe hearing impairment and cannot be corrected by hearing aids and (4) been admitted to ICU with radioactive material.

Sample size determination

Sample size calculation for the difference test in delirium incidence between the experimental and control groups was performed using G* Power 3.4. Based on a prior study, delirium incidence after sensory stimulation was 13%, while it was 25% in the standard care group, yielding an odds ratio of 0.57(8). For G* Power's two-sample proportion (McNemar) calculation, the study established a significance level of $\alpha = 0.05$ and a test power of Power =

0.8. Additionally, to account for factors such as patient mortality and loss to follow-up in the ICU, and considering a 20% dropout rate, this study intends to recruit a total of 324 participants, with 162 participants in each group.

Randomisation and allocation concealment

We utilised a paired randomization method to match eligible participants based on a validated delirium risk scoring model for ICU patients. The scores ranged from 0 to 1, and patients with similar risk scores were paired. For example, Patient A, a 62-year-old male with an APACHE-II score of 14, had a risk score of 0.33, while Patient B, a 56-year-old male with an APACHE-II score of 16, had a risk score of 0.32. Therefore, Patients A and B exhibited similar scores. Next, random numbers were generated using the randomisation.com website, and based on these generated random numbers, the paired subjects were randomly allocated to either the intervention group or the control group. Concealed allocation, achieved through using consecutively numbered, sealed and opaque envelopes, will be performed by a research assistant with no further involvement in the research after participant enrollment.

Blinding

Owing to the nature of the intervention, the researchers responsible for delivering the intervention will be aware of the group assignment. However, the outcome assessors will remain blinded to the group allocation and will not participate in data analysis or result reporting.

Intervention

Participants allocated to the intervention group will receive a VR-based sensory stimulation intervention plus usual care. This intervention is designed to provide VR-based visual and auditory stimulation to ICU patients, with additional support from family caregivers. The intervention will be administered by researchers who are trained ICU nurses. It will commence upon the patient's admission and continue until the fourteenth day of their ICU hospitalization or

the day of discharge if their stay is less than 14 days. Each day, a 30-minute session will be conducted (23–25).

The investigator will provide a delirium knowledge leaflet and a sample reorientation message to family caregivers in the intervention group. The investigator will spend 30 minutes explaining the contents to family caregivers during their first meeting. Family caregivers will be asked to prepare the family photographs, family video or recording at their earliest convenience. The leaflet contains information about the definition, prevalence and risk factors of delirium, along with practical steps family caregivers can take to support the patients. These steps include engaging in simple conversations, reminding patients of the current time, date, and location, providing glasses or hearing aids when necessary, decorating patient beds with family photographs, and discussing familiar topics. The reorientation messages serve to help patients understand their surroundings and offer encouragement. Each segment of the message requires two minutes for recording, following the sample message. The leaflet was designed by the investigator, and the sample reorientation message was adapted from a previous study(25). Both the leaflet and the sample orientation message were reviewed by a committee comprising three ICU nurse specialists, two nurse academics, one physician and two family caregivers.

Each daily session will commence at the earliest available daytime hour, typically between 12:00 and 16:00, following the completion of family recordings. During the pre-bedside phase, the investigator will gather family photographs, recordings, and videos, either digitally recorded or retrieved from previous family collections stored on electronic devices. Subsequently, the investigator will spend 30 minutes with each patient in the intervention group, tailoring the intervention based on the patient's ability to engage with auditory or visual stimulation (Figure 2). Notably, the intervention will be discontinued for trial participants under conditions such as participant requests or fluctuations in disease status.

Implementation Content: The intervention consists of the following stages: ① Guidance Stage (2 minutes): Introducing the content and purpose of the VR scenes to be played in the next 30 minutes; ② Relaxation Stage (5 minutes): Selecting natural scenery VR scenes accompanied by soothing background music to help patients relax; ③ Family and Friends Support Stage (18 minutes): Playing VR scene videos provided by family and friends, selecting happy moments and conveying family wishes and blessings; ④ Feedback Stage (5 minutes): Guiding patients to provide feedback and collecting relevant parameters, such as heart rate, respiration, pain, etc.

Control group

Participants in the control group will receive the usual care, consistent with their existing or planned treatment routines. Registered ICU nurses will administer the same nursing care, which includes, but is not limited to, sedation, analgesia, spontaneous breathing trials, indwelling catheter management, feeding, and bowel care.

Outcome and outcome measures

The research will measure the following outcomes. See **Table 1**.

Table 1 Outcomes and time schedules for data collection

Outcome Measures	Data Collection Time Points							Endpoint
	Day1	Day2	Day3	..	..	..	Day14 / Discharge	6 Months Post-Discharge
Delirium Score (CAM-ICU)	X	X	X	..	..	..	X	
Sedation Score (RASS)	X	X	X	..	..	..	X	
Pain Score (NRS)	X	X	X	..	..	..	X	
Pain Score (BPAT)	X	X	X	..	..	..	X	
Sleep (RCSQ)								

	X	X	X	..	..	..	X		
Post-traumatic stress disorder (PCL)							X		
ICU Memory (ICUMT)							X		
Patient Clinical Outcomes							X		
Quality of Life Score (EuroQol)	X						X		X
Independence Function (motor-FIM)	X						X		X
Cognitive function (cognitive-FIM)	X						X		X

Note: CAM-ICU, Confusion Assessment Methods for Intensive Care Units; RASS, Richmond Agitation-Sedation Scale; NRS, numerical rating scale; BPAT, behavior pain assessment tool; RCSQ, Richards-Campbell Sleep Questionnaire; PCL, Posttraumatic Stress Disorder Checklist; ICUMT, Intensive Care Unit Memory Tool; EuroQol, European Health Index; FIM, Functional Independence Measure;

Primary outcomes

Delirium incidence and duration

Delirium incidence means the number of patients who are delirious, which will be measured using the Confusion Assessment Methods for the Intensive Care Units (CAM-ICU) flow sheet. The CAM-ICU is comprised of four features, namely fluctuation of mental status, inattention, altered level of consciousness, and disorganised thinking. CAM-ICU was commonly adopted in ICU settings to measure delirium and was reported to have good interrater reliability (overall kappa coefficient = 0.71)(26).

Delirium duration

The delirium duration will be calculated when the patient is first considered to have delirium to the last time that patient is not supposed to have delirium based on CAM-ICU. The delirium will be measured every eight hours during patients' stay using CAM-ICU.

Delirium Severity

CAM-ICU-7 Delirium Severity Scale is a 7-point rating scale derived from the CAM-ICU and Richmond Agitation-Sedation Scale (RASS) assessments. The final CAM-ICU-7 score ranges from 0-7 with 7 being most severe. CAM-ICU-7 scores are further categorised as 0-2: no delirium, 3-5: mild to moderate delirium, and 6-7: severe delirium. CAM-ICU-7 showed a high internal consistency (Cronbach's α = 0.85) and good correlation with Delirium Rating Scale-Revised - 98 (DRS-R-98) (correlation coefficient = 0.64)(27).

Secondary outcomes

RCSQ

The Richards-Campbell Sleep Questionnaire (RCSQ) is employed to assess the sleep quality of ICU patients. Originally developed for evaluating sleep in critically ill patients, this questionnaire is designed to capture various aspects of sleep during the ICU stay. The scale evaluates perceptions of sleep depth, sleep onset latency, number of awakenings, time spent awake, and overall sleep quality. The content validity of the Chinese version of the RCSQ questionnaire is 0.840, and the Cronbach's α coefficient is 0.874.

PTSD

The 17-item PTSD Checklist (PCL) correspond to the DSM-III-R symptoms of PTSD and serves as a self-report scale for assessing PTSD(28,29). Patients will be asked to rate their agreement with each item on a scale from one (not at all) to five (extremely). PTSD-symptoms are categorized into re-experiencing (flashback, nightmare, emotional cue reactivity, and physical cue reactivity), avoidance and emotional numbing (avoidance of thoughts and reminders, amnesia, loss of interest, detachment, restricted affect, and foreshortened future), and hyperarousal (irritability/anger, sleep disturbance, difficulty concentrating, hypervigilance, exaggerated startle response). The total score ranges from 17 to 85(30).

A previous study confirmed the good reliability and validity of the PCL, including test-retest reliability of 0.96, internal consistency reliability of 0.94, and predictive validity of 0.64(31). High correlations with the Symptom Checklist-90 further confirm its reliability and validity(32).

ICU memory

The ICU-Memory Tool (ICU-M) will be used to measure ICU patients' ICU experience(33). This tool includes 14 questions (five open-ended questions and nine closed-ended questions), and is primarily divided into three parts: memories before admission to the ICU; memories during the ICU stay and memories after transferring out of the ICU. Memories during the ICU stay are categorized into three subscales: factual memories (lights, alarms, voices, families, faces, breathing tube, suctioning, darkness, clock, tube in your mouth, and wound care), memories of feelings (discomfort, confusion, sadness, anxiety/fear, panic, and pain), and memories of delusions (feeling that people were trying to hurt you, hallucinations, nightmares, dreams). The total number of memories in each of the three subscales will be summed. The Chinese version of ICU-M has a Cronbach's α coefficient of 0.823 and a scale-level content validity index of 0.946, confirming its good reliability and validity(34).

Patients' clinical outcomes

Medical outcomes will be extracted by the outcome assessor from the electronic health care system upon participants' discharge. This information includes: (a) ICU length of stay: the total number of days a patient stays in ICU; (b) 30-day mortality: the total death cases among all eligible cases at 30 days after admission to ICU; (c) duration of mechanical ventilation: the registered time in hours that the patients are on the mechanical ventilator; (d) the duration of use of physical restraint: the recorded time in hours that the patients are receiving physical restraint;

(e) sedation use: the documented total amount and average doses (mg/ per day) of sedation by using the conversion measurement of the same quantity of dexmedetomidine. (f) analgesics use: the documented total amount and average doses (mg/ per day) of analgesics using the conversion measurement of the same quantity of propofol. (g) self-extubation: the documented amount of self-extubation cases; (h) ICU acquired infection: the documented amount of self-acquired infection cases.

Quality of life

The EuroQol- 5 Dimension (EQ-5D) will be used to assess the participants' quality of life. It assigns a grade on a scale ranging from 0 (representing the worst possible health status) to 100 (representing the best possible health status) based on one question for each of the five dimensions, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression(35).

Independence and cognitive function

FIM (Functional Independence Measure) will be used to measure both the independence and cognitive function. The FIM is comprised of 18 items, which are grouped into two subscales: motor and cognition. The motor items are adapted from the Barthel Index and are collectively known as the Motor-FIM. These items includes: Eating, Grooming, Bathing, Dressing (upper body), Dressing (lower body), Toileting, Bladder management, Bowel management, Transfers (bed/chair/wheelchair), Transfers (toilet), Transfers (bath/shower), Walk/wheelchair, and Stairs. The cognition subscale, known as the Cognitive-FIM, includes the following items: Comprehension, Expression, Social interaction, Problem solving, and Memory. Each item is scored on a 7-point ordinal scale, ranging from a score of 1 to 7. A higher score indicates greater independence in performing the task associated with that item. The

Inter-Rater Reliability of FIM has been established with acceptable psychometric performance, with Intraclass corelation coefficients ranging from 0.86 to 0.88. Concurrent validity with the Barthel Index (ICC > 0.83) have demonstrated strong construct validity between items on Barthel Index and items on the FIM the measure functional limitations (36).

Sociodemographic and clinical information

Sociodemographic and clinical information including ICU patients and family caregivers' age, gender, educational level, marital status, occupation, the relationship between ICU patients and family caregivers, and the health history of ICU patients will be collected.

Table 2 Content of process evaluation and intervention integrity

Session	Content	Content Description
Pre-Implementation	Clarify Team Member Roles	Define roles for team members including software requirements, software testing, case selection, recruitment, intervention training, intervention implementation, outcome assessment, data management, statistics, and supervision personnel.
	Organize Research Member Training	Provide standardised training for intervention personnel to ensure consistency in the intervention program.
	Prepare Materials	Develop intervention implementation guidelines, flowcharts, intervention logs, and intervention checklists.
Implementation	Detailed Recording	Record the implementation process and any omissions using intervention logs.
	Supervision Auditing	Conduct process audits of the intervention by a nurse manager not involved in the research.
	Regular Reporting	Provide regular project progress reports, assess the evaluation, and make necessary research adjustments.
	Fidelity	Assess the adherence to intervention elements, dosage, and protocols.
Post-Implementation	Standardized Information Management	Double-check and enter follow-up questionnaires.
	Identify and Correct Errors	Correct errors by manually checking the original dataset, using box plots, histograms, and scatter plots, and using descriptive statistics.

Session	Content	Content Description
	Handling Missing Data	Supplement missing data through participant contact and medical record queries.
	Analyze Statistic Differences	Compare observed and unobserved statistical differences.
	Use Intention-to-Treat (ITT) Analysis	Perform analysis using the intention-to-treat approach.

Data collection

The principal investigator will begin by explaining the study and obtaining written informed consent from the participants. Afterward, a research assistant, who is a postgraduate student majoring in nursing, will proceed to retrieve patients' demographic data from their medical records and collect information on their quality of life, independence, and cognitive function prior to admission to the ICU from the participants' family caregivers. The nurses in charge of the study ICU will assess the CAM-ICU, RASS, RCSQ during daily routine. On the fourteenth day of a patient's ICU hospitalization, or upon discharge if the ICU stay is less than 14 days, the research assistant will collect data on secondary measures (PTSD, ICU memory), clinical outcomes, independence, and cognitive function. Additionally, quality of life, independence, and cognitive function will be assessed via a phone call by the research assistant six months after the completion of the intervention.

Data management

To identify and rectify errors, such as missing values, outliers, and typos, data cleaning strategies will be employed(37). Several methods will be employed to detect errors and minimise the impacts on the accuracy of results. Firstly, the original dataset (in Excel) will be manually checked to identify data error. Secondly, statistical graphical explorations including box plots,

histograms and scatter plots, along with descriptive statistics such as mean, frequency, and percentage, will be used. Through this process, data errors, including typos, outliers, and violations of integrity constraints, will be corrected.

Data analysis

This study will use SPSS 25.0 and R 23.0 software for data analysis. All statistical tests will be two-tailed, with the significance level set at 0.05. To assess the normal distribution of continuous variables, skewness, kurtosis, Q-Q plots, and histograms will be examined. Variables with skewness and kurtosis values within the range of -2.0 to 2.0 will be considered to have a normal distribution. For normally distributed continuous variables, the study will describe them using the mean ± standard deviation (Mean ± SD). For variables that do not meet the normal distribution criteria, the study will describe them using the median (interquartile range, IQR). Categorical variables will be described using frequency (proportion). If the assumptions for hypothesis testing of continuous variables are met, paired-sample t-tests will be used to compare differences between different groups. Otherwise, the paired Wilcoxon signed-rank test will be employed. For categorical variables, Kappa consistency tests and paired chi-square tests (McNemar's test) will be used to compare differences between different groups. Additionally, missing values will be imputed using multiple imputation methods.

The study will follow the intention-to-treat (ITT) principle for analysis. After imputing missing data using multiple imputation methods, the study will perform ITT analysis and report relevant uncertainty indicators, such as confidence intervals and standard errors, in the results. Furthermore, this study will use mixed-effects models to analyze differences between groups in delirium duration, delirium severity, psychological outcomes, and other outcomes.

DISCUSSION

This study aims to evaluate the effects of a VR-based sensory stimulation on preventing delirium and improving various patient outcomes, including psychological measures (sleep quality, post-traumatic stress disorder, ICU memory), clinical outcomes (ICU length of stay), and other measures (quality of life, independence, and cognitive function).

The research team will follow the International Conference on Harmonization - Good Clinical Practice (ICH-GCP) and the Declaration of Helsinki. Ethical approval has been obtained from the Ethics Committee of the study hospital. Written consent will be acquired from eligible participants or their surrogates. All collected data will be kept strictly confidential and used exclusively for the purposes of this study. The research report will not contain any personal information of the participants.

The study has been registered in the Centre for Clinical Research and Biostatistics after obtaining ethical approval and before the recruitment of participants. Results of this RCT study will be disseminated via peer-reviewed journals and presentations at local, national and international conferences.

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Competing interests statement

The authors declare that they have no competing interests.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Word counts: 3453

Figure 1: Diagram of the flow of the study

Figure 2: Flowchart of VR-based sensory stimulation implementation

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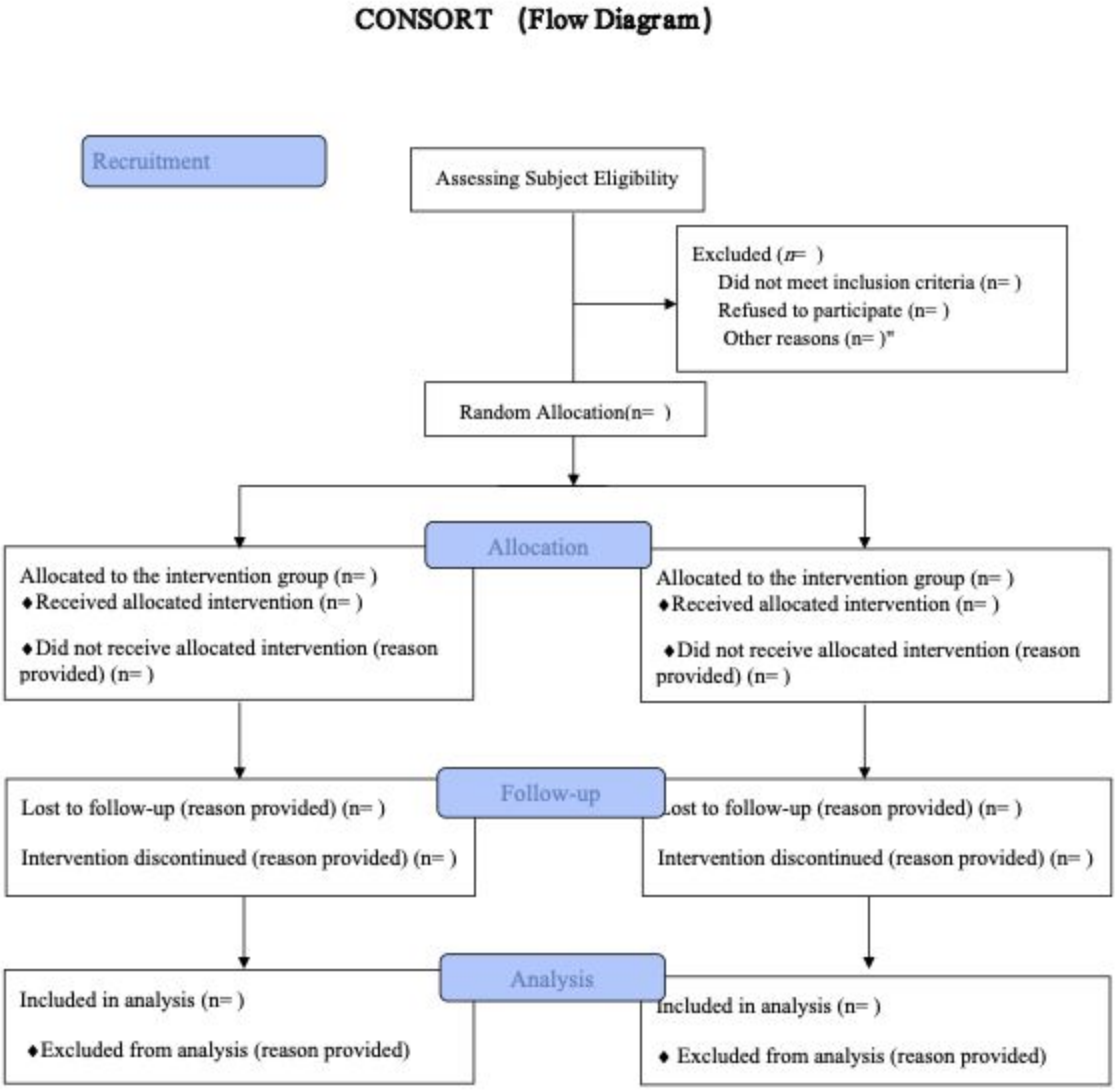

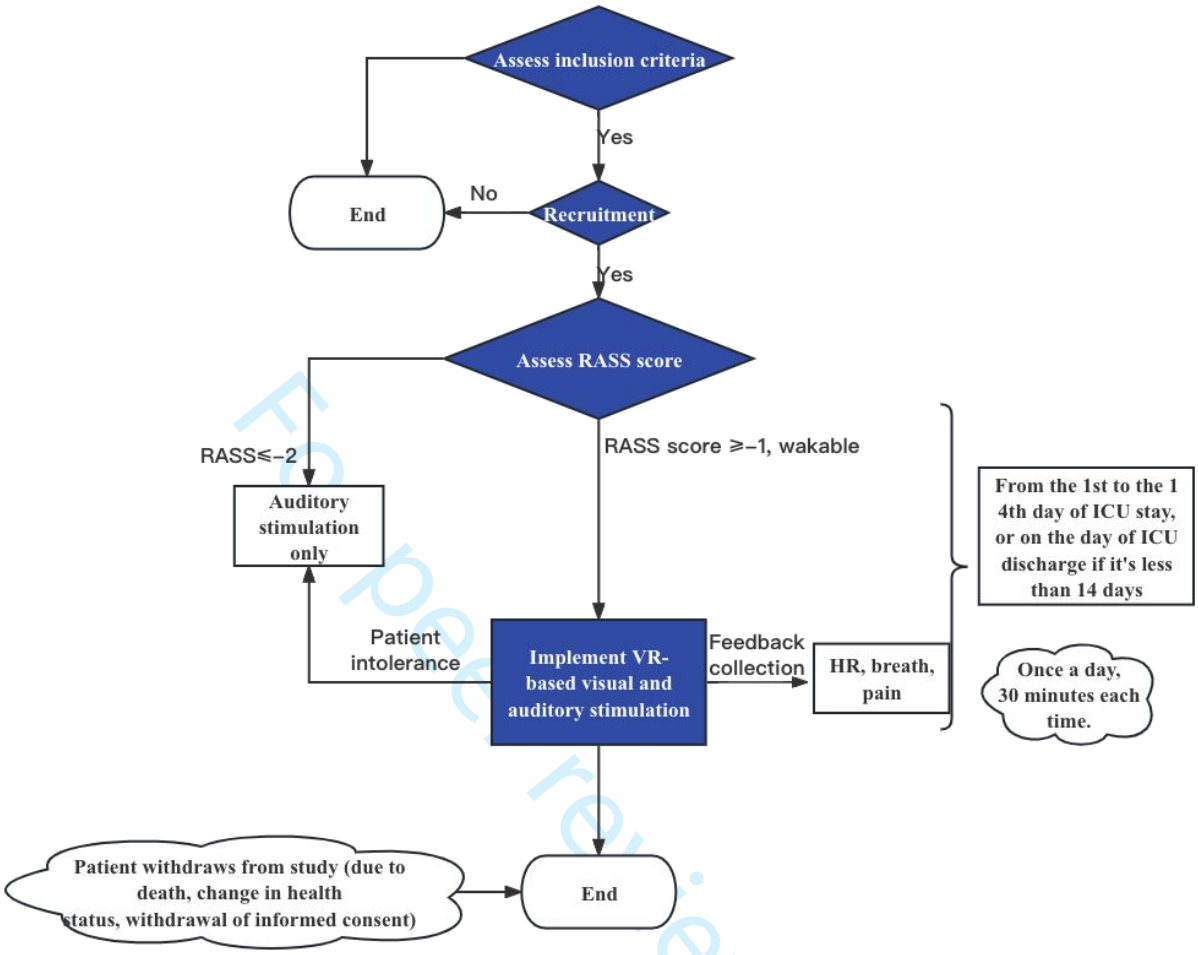

Title page

Title: Effectiveness of a Virtual Reality-based sensory stimulation intervention on preventing delirium in Intensive Care Units: a randomised controlled trial protocol

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This protocol was approved by Research Ethics Committee of Shenzhen Hospital of Southern Medical University (NYSZYYEC20230068).

Trial registration number ClinicalTrials.gov NCT06153472. Trial registration date: November 22, 2023

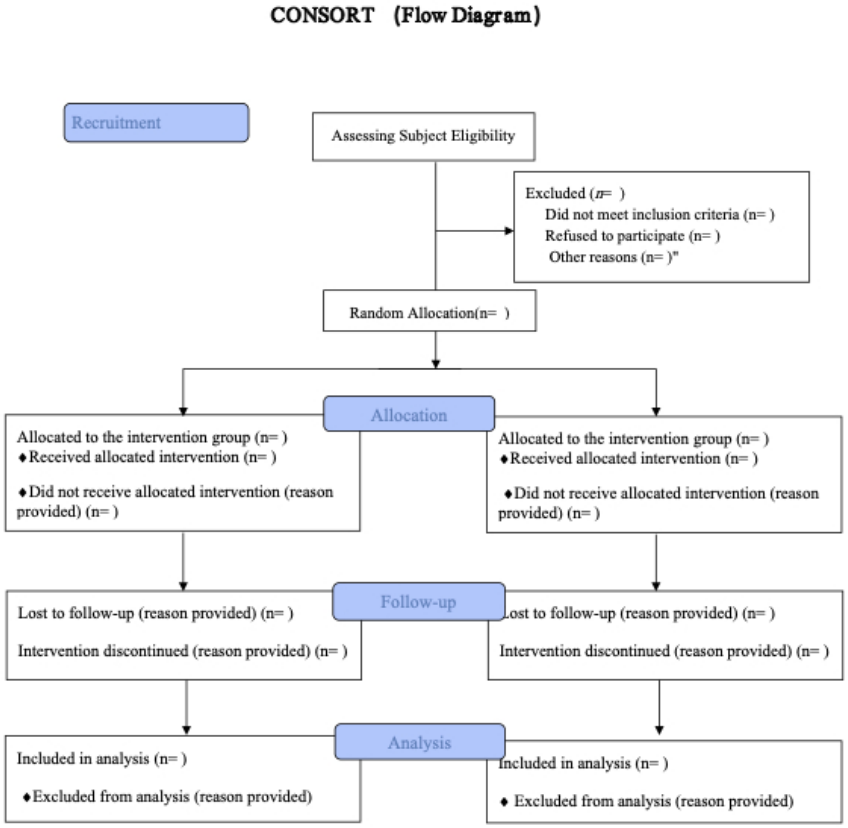

Figure 1: Diagram of the flow of the study

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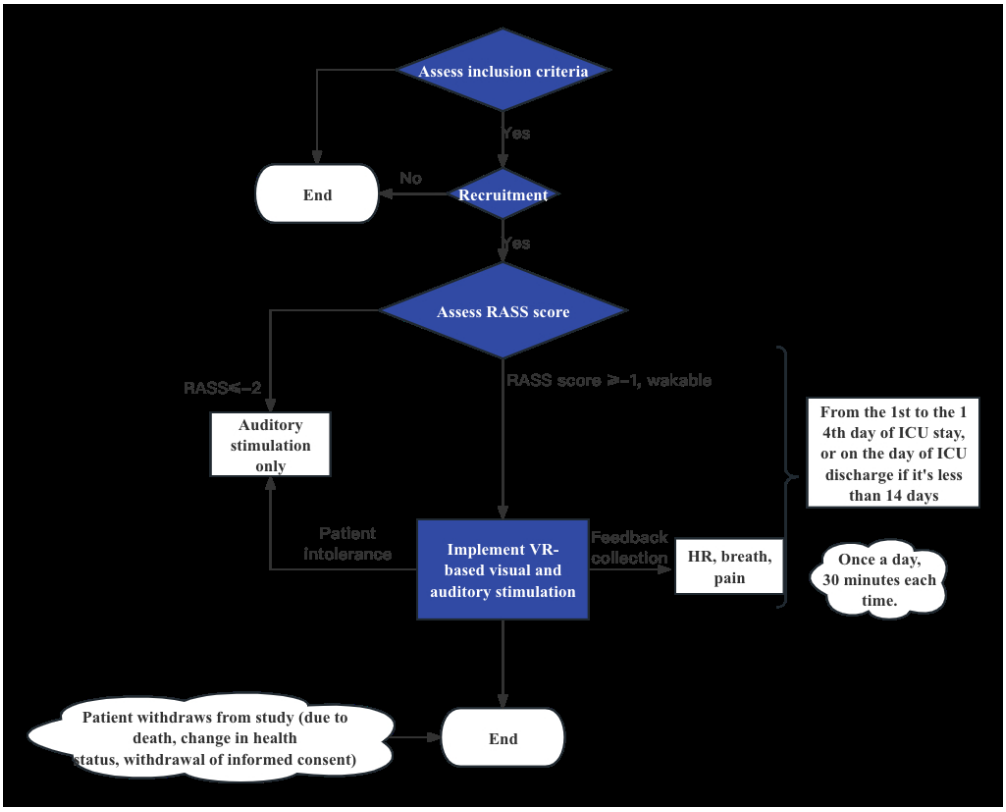

Figure 2: Flowchart of VR-based sensory stimulation implementation

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BMJ Open

Effectiveness of a Virtual Reality-Based Sensory Stimulation Intervention in Preventing Delirium in Intensive Care Units: A Randomized Controlled Trial Protocol

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Effectiveness of a Virtual Reality-Based Sensory Stimulation Intervention in Preventing Delirium in Intensive Care Units: A Randomized Controlled Trial Protocol

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Contributors SL, YL, DL, FT designed the study and wrote the manuscript. SL is the principal investigator and data management leader. MH, TW, and YL are members of the study team who contributed to the development of the study methods, and team members supervised the trial. All authors approved the final version of the manuscript.

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Competing interests None declared.

Patient consent for publication Not required.

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ABSTRACT

Introduction:

Delirium is a common acute cognitive impairment characterized by confusion, disorientation, and attention deficits, particularly prevalent in ICU settings. Given its significant impact on patients, caregivers, and healthcare resources, preventing delirium in ICU patients is of paramount importance. This is the first randomized controlled trial (RCT) designed to evaluate the effects of a Virtual Reality-based sensory stimulation intervention on preventing delirium in intensive care unit (ICU) patients.

Methods and Analysis:

We employed a paired randomization method to match eligible participants based on a validated delirium risk scoring model for ICU patients. The study will commence in September 2024 and conclude in June 2026. A consecutive sample of 324 ICU patients admitted to the study setting will be recruited. Eligible participants will be randomly allocated to receive either Virtual Reality-based sensory stimulation in addition to usual care or usual care alone. The Virtual Reality-based sensory stimulation intervention will last for up to fourteen days, with all interventions administered by a research team. We define delirium-free days over a 14-day period as the primary outcome. The secondary outcomes will include delirium incidence, duration, and severity, patients' psychological well-being (post-traumatic stress disorder, sleep quality, and ICU memory), patients' clinical outcomes, and other outcomes (quality of life, independence, and cognitive function). Data will be collected at baseline, post-intervention, and six months post-intervention. Two independent t-tests or Wilcoxon-Mann-Whitney tests will be utilized for continuous variables, while chi-square or Fisher's exact tests will be employed for categorical variables. The analysis will

adhere to both the intention-to-treat and per protocol principles. Additionally, mixed-effects models and subgroup analysis will be planned.

Ethics and dissemination This protocol was approved by Research Ethics Committee of Shenzhen Hospital of Southern Medical University (NYSZYYEC20230068). All participants or their family caregivers will provide written informed consent. Results will be disseminated through scientific publications, and presentations at local and international conferences.

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Keywords: Critical care; Delirium, Virtual Reality, Sensory stimulation

Article Summary

Strengths and limitations of this study

► This study evaluates a Virtual Reality-based sensory stimulation for preventing delirium and improving patients' psychological well-being (specifically post-traumatic stress disorder, sleep quality, and ICU memory), patients' clinical outcomes (including ICU length of stay), and other outcomes (such as quality of life, independence, and cognitive function).

►This study utilizes a rigorous randomized controlled trial design, incorporating a Virtual Reality-based sensory stimulation intervention for preventing delirium in ICUs. The methodological rigor of this design enhances the reliability and validity of our findings, providing valuable insights into the effectiveness of such interventions in clinical settings.

►Due to the nature of the intervention, blinding was only possible for the outcome assessors, while blinding for the participants and those delivering the intervention was not feasible.

INTRODUCTION

Delirium is a common acute state of cognitive confusion. Intensive Care Unit (ICU) delirium is highly prevalent, with an incidence ranging from 31%(1) to 56%(2), and it can be as high as 81%(3) in ICU patients undergoing mechanical ventilation. A preliminary analysis of data from 375 patients admitted to the ICU for more than 24 hours revealed an occurrence rate of 44% for ICU delirium(4). Moreover, delirious ICU patients had 1.33 times longer ICU stays and a 9.57-fold increase in mortality compared to non-delirious ICU patients(5). ICU patients who experience delirium may suffer from post-traumatic stress disorder, anxiety, depression, and cognitive impairment for up to two years(6).

Non-pharmacological preventive measures aim to reduce one or more modifiable risk factors for ICU delirium(7). Previous research identified sensory stimulation as a key and effective non-pharmacological intervention in preventing ICU delirium(8,9). Sensory stimulation involves activating one or more senses(10), with visual and auditory stimuli being particularly effective for ICU patients(11). To further investigate the effectiveness of sensory stimulation in preventing ICU delirium, the research team conducted an initial study to assess the implementation of sensory stimulation on preventing delirium in ICU and subsequently developed a sensory stimulation intervention plan(12,13). This plan involved daily sessions of 30 minutes each for seven days, including visual stimuli (displaying personal or family photos) and auditory stimuli (playing recordings of family members). The results of the study showed that sensory stimulation reduced the duration and severity of ICU delirium but did not significantly decrease the incidence of ICU delirium(8,9). The limited effectiveness of sensory stimulation may be attributed to the narrow range of stimuli, insufficient stimulus intensity, and inadequate dosing and implementation methods(9).

In contrast, Virtual Reality (VR) technology, characterized by its three-dimensional and highly immersive qualities, has the potential to provide more effective sensory stimulation by immersing participants in three-dimensional dynamic environments(14). International research suggests that VR offers significant advantages in sensory stimulation and could be a promising approach for preventing ICU delirium, however, it's important to note that studies on the use of VR in preventing ICU delirium are currently in the feasibility testing stage(15–17). The DREAMS project at the University of Florida in the United States investigated the effectiveness of VR and found that 95.6% of participants found it very comfortable, 51.9% reported improved sleep quality, and 81.5% experienced reduced pain(16). This team further conducted a study with 46 ICU patients, implementing a seven-day VR intervention, which resulted in reduced stress, pain, anxiety, and improved cognitive function and attention in the participants(17). Additionally, Jawed and colleagues conducted a preliminary trial that showed VR could alleviate anxiety in ICU patients(15). However, since those studies were in the feasibility testing stage, they were unable to measure the effects on reducing ICU delirium.

The stress recovery theory and attention restoration theory explain the principles behind preventing ICU delirium using VR-based sensory stimulation(18,19). The stress recovery theory suggests that natural environments support positive changes in emotional states and psychophysiological recovery, primarily by relaxing the parasympathetic nervous system (19). In stressful ICU environments, cognitive and attentional resources can become fatigued, which is especially crucial for critically ill patients facing stressors. The cognitive demands and overstimulation in the ICU environment contribute to mental fatigue and stress responses(19). On the other hand, the attention restoration theory suggests that exposure to natural environments requires fewer cognitive resources and promotes a sense of disengagement from stressors,

allowing attention to rest and recover(18). Therefore, VR-based visual and auditory stimuli, by immersing patients in relaxing VR environments, may have a protective effect against environmental stress and aid in the recovery of physiological, emotional, and attentional functions, thus preventing delirium. Chirico and colleagues further elucidated the mechanisms of VR-based sensory stimulation in delirium prevention: exposure to VR-based natural environments can trigger a specific psychophysiological pattern activated by the parasympathetic nervous system, leading to intense emotional reactions(20). Emotion responses increase with higher levels of immersion, which can be utilized to alleviate symptoms like anxiety, pain, and fear, effectively reducing patient stress, improving sleep quality, and consequently reducing the incidence of delirium(20).

Aim and hypothesis

This study aims to evaluate the effects of evaluates a Virtual Reality-based sensory stimulation on preventing delirium, and improving patients' psychological (post-traumatic stress disorder, sleep quality, ICU memory), patients' clinical (ICU length of stay) and other outcomes (quality of life, independence and cognitive function). And the comparator in our study is 'usual care,' representing the standard treatment or practices typically provided in similar clinical settings.

It is hypothesised that at patients' fourteenth day of ICU hospitalisation or the day of discharge (if the ICU stay is less than 14 days), will experience the following improvements compared with those receiving usual care.

1. ICU patients receiving the sensory stimulation intervention will have:
    a. A reduction in incidence, duration and severity of delirium.
    b. An improvement in their post-traumatic stress disorder.
    c. An improvement of factual memories.

d. A shorter length of ICU stay.

e. An improvement in quality of life, independence and cognitive function.

At six months after completing the intervention, compared to those receiving usual care, ICU patients undergoing the VR-based sensory stimulation intervention will experience an improvement in quality of life, independence, and cognitive function.

METHODS AND ANALYSIS

Design

A multi-center assessor-blinded two-arm parallel group RCT will be conducted. Figure 1 shows the study flow.

Setting

Participants will be recruited from general ICUs of Shenzhen Hospital of Southern Medical University and Shenzhen Hospital of Beijing University, two comprehensive tertiary A -level hospitals in Shenzhen, Guangdong province, Mainland China. Tertiary A-level hospital provides specialist tertiary care in a large hospital after a referral from primary and secondary care.(21)

Participants

All ICU patients admitted to the study setting will be recruited if they are/have: (1) aged 18 years or older, (2) first-time admission to the ICU, and (3) a Richmond Agitation-Sedation Scale (RASS) score of ≥-3(22) . Patients will be excluded if they have: (1) been diagnosed with dementia, delirium or acute psychiatric illness at admission, (2) been diagnosed with end-stage cancer, (3) severe hearing impairment and cannot be corrected by hearing aids and (4) been admitted to ICU with radioactive material.

Sample size determination

Sample size calculation for the difference test in delirium incidence between the experimental and control groups was performed using G* Power 3.4. Based on a prior study, delirium incidence after sensory stimulation was 13%, while it was 25% in the standard care group, yielding an odds ratio of 0.57(8). For G* Power's two-sample proportion (z-test) calculation, with a significance level set at $\alpha = 0.05$ and a desired test power of Power = 0.8, the required sample size was determined to be 259 participants. Additionally, to account for factors such as patient mortality and loss to follow-up in the ICU, and considering a 20% dropout rate, this study intends to recruit a total of 324 participants, with 162 participants in each group.

Randomisation and allocation concealment

We employed a simple randomization method by generating random numbers through the randomization.com website. Based on these generated numbers, participants were then randomly assigned to either the intervention or control group. To ensure allocation concealment, consecutively numbered, sealed, and opaque envelopes will be utilized. This process will be conducted by a research assistant who will have no further involvement in the study after participant enrollment.

Blinding

Owing to the nature of the intervention, the researchers responsible for delivering the intervention will be aware of the group assignment. However, the outcome assessors will remain blinded to the group allocation and will not participate in data analysis or result reporting.

Intervention

Participants allocated to the intervention group will receive a VR-based sensory stimulation intervention plus usual care. This intervention is designed to provide VR-based visual and

auditory stimulation to ICU patients, with additional support from family caregivers. The intervention will be administered by researchers who are trained ICU nurses. It will commence upon the patient's admission and continue until the fourteenth day of their ICU hospitalization or the day of discharge if their stay is less than 14 days. Each day, a 30-minute session will be conducted (23–25).

The investigator will provide a delirium knowledge leaflet and a sample reorientation message to family caregivers in the intervention group. The investigator will spend 30 minutes explaining the contents to family caregivers during their first meeting. Family caregivers will be asked to prepare the family photographs, family video or recording at their earliest convenience. The leaflet contains information about the definition, prevalence and risk factors of delirium, along with practical steps family caregivers can take to support the patients. These steps include engaging in simple conversations, reminding patients of the current time, date, and location, providing glasses or hearing aids when necessary, decorating patient beds with family photographs, and discussing familiar topics. The reorientation messages serve to help patients understand their surroundings and offer encouragement. Each segment of the message requires two minutes for recording, following the sample message. The leaflet was designed by the investigator, and the sample reorientation message was adapted from a previous study(25). Both the leaflet and the sample orientation message were reviewed by a committee comprising three ICU nurse specialists, two nurse academics, one physician and two family caregivers.

Each daily session will commence at the earliest available daytime hour, typically between 12:00 and 16:00, following the completion of family recordings. During the pre-bedside phase, the investigator will gather family photographs, recordings, and videos, either digitally recorded or retrieved from previous family collections stored on electronic devices. Subsequently, the investigator will spend 30 minutes with each patient in the intervention group,

tailoring the intervention based on the patient's ability to engage with auditory or visual stimulation (Figure 2). Notably, the intervention will be discontinued for trial participants under conditions such as participant requests or fluctuations in disease status.

Implementation Content: The intervention consists of the following stages: ① Guidance Stage (2 minutes): Introducing the content and purpose of the VR scenes to be played in the next 30 minutes; ② Relaxation Stage (5 minutes): Selecting natural scenery VR scenes accompanied by soothing background music to help patients relax; ③ Family and Friends Support Stage (18 minutes): Playing VR scene videos provided by family and friends, selecting happy moments and conveying family wishes and blessings; ④ Feedback Stage (5 minutes): Guiding patients to provide feedback and collecting relevant parameters, such as heart rate, respiration, pain, etc.

Control group

Participants in the control group will receive the usual care, consistent with their existing or planned treatment routines. Registered ICU nurses will administer the same nursing care, which includes, but is not limited to, sedation, analgesia, spontaneous breathing trials, indwelling catheter management, feeding, and bowel care.

Outcome and outcome measures

The research will measure the following outcomes. See **Table 1**.

Table 1 Outcomes and time schedules for data collection

Outcome Measures	Data Collection Time Points							Endpoint
	Day1	Day2	Day3	..	..	..	Day14 / Discharge	6 Months Post-Discharge
Delirium Score (CAM-								

ICU)	X	X	X	..	..	..	X	
Sedation Score (RASS)	X	X	X	..	..	..	X	
Pain Score (NRS)	X	X	X	..	..	..	X	
Pain Score (BPAT)	X	X	X	..	..	..	X	
Sleep (RCSQ)	X	X	X	..	..	..	X	
Post-traumatic stress disorder (PCL)							X	
ICU Memory (ICUMT)							X	
Patient Clinical Outcomes							X	
Quality of Life Score (EuroQol)	X						X	X
Independence Function (motor-FIM)	X						X	X
Cognitive function (cognitive-FIM)	X						X	X

Note: CAM-ICU, Confusion Assessment Methods for Intensive Care Units; RASS, Richmond Agitation-Sedation Scale; NRS, numerical rating scale; BPAT, behavior pain assessment tool; RCSQ, Richards-Campbell Sleep Questionnaire; PCL, Posttraumatic Stress Disorder Checklist; ICUMT, Intensive Care Unit Memory Tool; EuroQol, European Health Index; FIM, Functional Independence Measure;

Primary outcomes

Delirium-free days

Our primary outcome will be delirium-free days over a 14-day period, with delirium assessed using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) flow sheet. The CAM-ICU is comprised of four features, namely fluctuation of mental status, inattention, altered level of consciousness, and disorganised thinking. CAM-ICU was commonly adopted in ICU settings to measure delirium and was reported to have good interrater reliability (overall kappa coefficient = 0.71)(26).

Secondary outcomes

Delirium incidence, duration and severity

Delirium incidence refers to the number of patients exhibiting delirium. Delirium duration is calculated from the initial delirium diagnosis to the last assessment indicating the absence of delirium, based on CAM-ICU evaluations conducted every eight hours during the patient's stay. Delirium duration will be measured for each shift and summarized in days. Delirium Severity will be measured by CAM-ICU-7 Delirium Severity Scale, which is a 7-point rating scale derived from the CAM-ICU and Richmond Agitation-Sedation Scale (RASS) assessments. The final CAM-ICU-7 score ranges from 0-7 with 7 being most severe. CAM-ICU-7 scores are further categorised as 0-2: no delirium, 3-5: mild to moderate delirium, and 6-7: severe delirium. CAM-ICU-7 showed a high internal consistency (Cronbach's α = 0.85) and good correlation with Delirium Rating Scale-Revised - 98 (DRS-R-98) (correlation coefficient = 0.64)(27). The highest CAM-ICU-7 score recorded over the 14-day period will represent delirium severity.

RCSQ

The Richards-Campbell Sleep Questionnaire (RCSQ) is employed to assess the sleep quality of ICU patients. Originally developed for evaluating sleep in critically ill patients, this questionnaire is designed to capture various aspects of sleep during the ICU stay. The scale evaluates perceptions of sleep depth, sleep onset latency, number of awakenings, time spent awake, and overall sleep quality. The content validity of the Chinese version of the RCSQ questionnaire is 0.840, and the Cronbach's α coefficient is 0.874.

PTSD

The 17-item PTSD Checklist (PCL) correspond to the DSM-III-R symptoms of PTSD and serves as a self-report scale for assessing PTSD(28,29). Patients will be asked to rate their agreement with each item on a scale from one (not at all) to five (extremely). PTSD-symptoms are

categorized into re-experiencing (flashback, nightmare, emotional cue reactivity, and physical cue reactivity), avoidance and emotional numbing (avoidance of thoughts and reminders, amnesia, loss of interest, detachment, restricted affect, and foreshortened future), and hyperarousal (irritability/anger, sleep disturbance, difficulty concentrating, hypervigilance, exaggerated startle response). The total score ranges from 17 to 85(30).

A previous study confirmed the good reliability and validity of the PCL, including test-retest reliability of 0.96, internal consistency reliability of 0.94, and predictive validity of 0.64(31). High correlations with the Symptom Checklist-90 further confirm its reliability and validity(32).

ICU memory

The ICU-Memory Tool (ICU-M) will be used to measure ICU patients' ICU experience(33). This tool includes 14 questions (five open-ended questions and nine closed-ended questions), and is primarily divided into three parts: memories before admission to the ICU; memories during the ICU stay and memories after transferring out of the ICU. Memories during the ICU stay are categorized into three subscales: factual memories (lights, alarms, voices, families, faces, breathing tube, suctioning, darkness, clock, tube in your mouth, and wound care), memories of feelings (discomfort, confusion, sadness, anxiety/fear, panic, and pain), and memories of delusions (feeling that people were trying to hurt you, hallucinations, nightmares, dreams). The total number of memories in each of the three subscales will be summed. The Chinese version of ICU-M has a Cronbach's α coefficient of 0.823 and a scale-level content validity index of 0.946, confirming its good reliability and validity(34).

Patients' clinical outcomes

Medical outcomes will be extracted by the outcome assessor from the electronic health care system upon participants' discharge. This information includes: (a) ICU length of stay: the total number of days a patient stays in ICU; (b) 30-day mortality: the total death cases among all eligible cases at 30 days after admission to ICU; (c) duration of mechanical ventilation: the registered time in hours that the patients are on the mechanical ventilator; (d) the duration of use of physical restraint: the recorded time in hours that the patients are receiving physical restraint; (e) sedation use: the documented total amount and average doses (mg/ per day) of sedation by using the conversion measurement of the same quantity of dexmedetomidine. (f) analgesics use: the documented total amount and average doses (mg/ per day) of analgesics using the conversion measurement of the same quantity of propofol. (g) self-extubation: the documented amount of self-extubation cases; (h) ICU acquired infection: the documented amount of self-acquired infection cases.

Quality of life

The EuroQol- 5 Dimension (EQ-5D) will be used to assess the participants' quality of life. It assigns a grade on a scale ranging from 0 (representing the worst possible health status) to 100 (representing the best possible health status) based on one question for each of the five dimensions, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression(35).

Independence and cognitive function

FIM (Functional Independence Measure) will be used to measure both the independence and cognitive function. The FIM is comprised of 18 items, which are grouped into two subscales:

motor and cognition. The motor items are adapted from the Barthel Index and are collectively known as the Motor-FIM. These items includes: Eating, Grooming, Bathing, Dressing (upper body), Dressing (lower body), Toileting, Bladder management, Bowel management, Transfers (bed/chair/wheelchair), Transfers (toilet), Transfers (bath/shower), Walk/wheelchair, and Stairs. The cognition subscale, known as the Cognitive-FIM, includes the following items: Comprehension, Expression, Social interaction, Problem solving, and Memory. Each item is scored on a 7-point ordinal scale, ranging from a score of 1 to 7. A higher score indicates greater independence in performing the task associated with that item. The Inter-Rater Reliability of FIM has been established with acceptable psychometric performance, with Intraclass corelation coefficients ranging from 0.86 to 0.88. Concurrent validity with the Barthel Index (ICC > 0.83) have demonstrated strong construct validity between items on Barthel Index and items on the FIM the measure functional limitations (36).

Sociodemographic and clinical information

Sociodemographic and clinical information including ICU patients and family caregivers' age, gender, educational level, marital status, occupation, the relationship between ICU patients and family caregivers, and the health history of ICU patients will be collected.

Table 2 Content of process evaluation and intervention integrity

Session	Content	Content Description
Pre-Implementation	Clarify Team Member Roles	Define roles for team members including software requirements, software testing, case selection, recruitment, intervention training, intervention implementation, outcome assessment, data management, statistics, and supervision personnel.

Session	Content	Content Description
	Organize Research Member Training	Provide standardised training for intervention personnel to ensure consistency in the intervention program.
	Prepare Materials	Develop intervention implementation guidelines, flowcharts, intervention logs, and intervention checklists.
Implementation	Detailed Recording	Record the implementation process and any omissions using intervention logs.
	Supervision Auditing	Conduct process audits of the intervention by a nurse manager not involved in the research.
	Regular Reporting	Provide regular project progress reports, assess the evaluation, and make necessary research adjustments.
	Fidelity	Assess the adherence to intervention elements, dosage, and protocols.
Post-Implementation	Standardized Information Management	Double-check and enter follow-up questionnaires.
	Identify and Correct Errors	Correct errors by manually checking the original dataset, using box plots, histograms, and scatter plots, and using descriptive statistics.
	Handling Missing Data	Supplement missing data through participant contact and medical record queries.
	Analyze Statistic Differences	Compare observed and unobserved statistical differences.

Session	Content	Content Description
	Use Intention-to-Treat (ITT) Analysis	Perform analysis using the intention-to-treat approach.

Data collection

Two research assistants, both trained consistently, will commence by explaining the study and obtaining written informed consent from the participants. Subsequently, an ICU nurse with a master's degree and a postgraduate student specializing in nursing will gather patients' demographic data from their medical records and collect information on their quality of life, independence, and cognitive function prior to admission to the ICU from the participants' family caregivers. The nurses in charge of the study ICU will assess the CAM-ICU, RASS, RCSQ during daily routine. On the fourteenth day of a patient's ICU hospitalization, or upon discharge if the ICU stay is less than 14 days, the research assistant will collect data on secondary measures (PTSD, ICU memory), clinical outcomes, independence, and cognitive function. Additionally, quality of life, independence, and cognitive function will be assessed via a phone call by the research assistant six months after the completion of the intervention. Notably,
Two research centers each have two research assistants dedicated to obtaining informed consent and collecting data, respectively.

Data management

Each patient has a case report form (CRF) for data collection, initially documented on paper. Following this, the data from the CRFs are transferred to Excel spreadsheets on computers. Access to the Excel files will be restricted through password protection. Only authorized personnel participating in the study will have access to these files. All data entry and manipulation activities will be logged and tracked to maintain transparency and accountability.

To identify and rectify errors, such as missing values, outliers, and typos, data cleaning strategies will be employed(37). Several methods will be employed to detect errors and minimise the impacts on the accuracy of results. Firstly, the original dataset (in Excel) will be manually checked to identify data error. Secondly, statistical graphical explorations including box plots, histograms and scatter plots, along with descriptive statistics such as mean, frequency, and percentage, will be used. Through this process, data errors, including typos, outliers, and violations of integrity constraints, will be corrected.

Data analysis

This study will utilize R4.3.2 software for data analysis, with statistical analysis led by two master's degree-holding research personnel. All statistical tests will be two-tailed, with the significance level set at 0.05. To assess the normal distribution of continuous variables, skewness, kurtosis, Q-Q plots, and histograms will be examined. Variables with skewness and kurtosis values within the range of -2.0 to 2.0 will be considered to have a normal distribution. For normally distributed continuous variables, the study will describe them using the mean ± standard deviation (Mean ± SD). For variables that do not meet the normal distribution criteria, the study will describe them using the median (interquartile range, IQR). Categorical variables will be described using frequency (proportion). If the assumptions for hypothesis testing of continuous variables are met, independent two-sample t-tests will be used to compare differences between different groups. Otherwise, the Wilcoxon-Mann-Whitney will be employed. For categorical variables, chi-square tests and Fisher's exact tests will be used to compare differences between different groups. Additionally, missing values will be imputed using multiple imputation methods. The study will follow the intention-to-treat (ITT) and per-protocol (PP) principle for analysis. After imputing missing data using multiple imputation methods, the study

will perform ITT and PP analysis and report relevant uncertainty indicators, such as confidence intervals and standard errors, in the results. This study will employ mixed-effects models for outcomes with repeated measurements. These models, also known as multilevel or hierarchical models, are effective for analyzing data with a hierarchical structure, such as repeated measurements. Fixed effects will estimate population-level relationships between predictors and outcomes. Our study will include predictors like APACHE-II score, age, admission category, and use of sedatives and analgesics as fixed explanatory variables. Subgroup analyses based on age, gender, and length of ICU stay will be conducted.

DISCUSSION

This study evaluates a Virtual Reality-based sensory stimulation for preventing delirium and improving patients' psychological well-being (specifically post-traumatic stress disorder, sleep quality, and ICU memory), patients' clinical outcomes (including ICU length of stay), and other outcomes (such as quality of life, independence, and cognitive function). It employs a rigorous randomized controlled trial design, incorporating a Virtual Reality-based sensory stimulation intervention within ICUs, which enhances the reliability and validity of findings. The methodological rigor of this design provides valuable insights into the effectiveness of such interventions in clinical settings.

In our study, our primary focus is on preventing delirium. However, if delirium does occur, physicians may prescribe antipsychotic medications. We will accurately document whether patients receive these medications and the dosage administered. Furthermore, we will maintain detailed records of the dosage of sedatives and analgesics administered to patients throughout the study.

Due to the nature of the intervention, blinding was only possible for the outcome assessors, while blinding for the participants and those delivering the intervention was not feasible.

The study anticipates prompt availability of materials from family members and has contingency plans in place to ensure timely initiation of the VR intervention. However, delays in obtaining materials from family members may occur, potentially impacting the initiation of the VR intervention. Additionally, the use of antipsychotic medications to manage delirium may influence study outcomes, and while their administration will be documented, their effects on study outcomes may not be fully controlled.

Funding statement

This study has received support from the China Postdoctoral Science Foundation (2023M731551) and the Science and Technology Project of Shenzhen (JCYJ20230807142300002).

Competing interests statement

The authors declare that they have no competing interests.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Contributors

SL, YL, DL, FT designed the study and wrote the manuscript. SL is the principal investigator and data management leader. MH, TW, and YL are members of the study team who contributed to the development of the study methods, and team members supervised the trial. All authors approved the final version of the manuscript.

Word counts: 3453

Figure 1: Diagram of the flow of the study

Figure 2: Flowchart of VR-based sensory stimulation implementation

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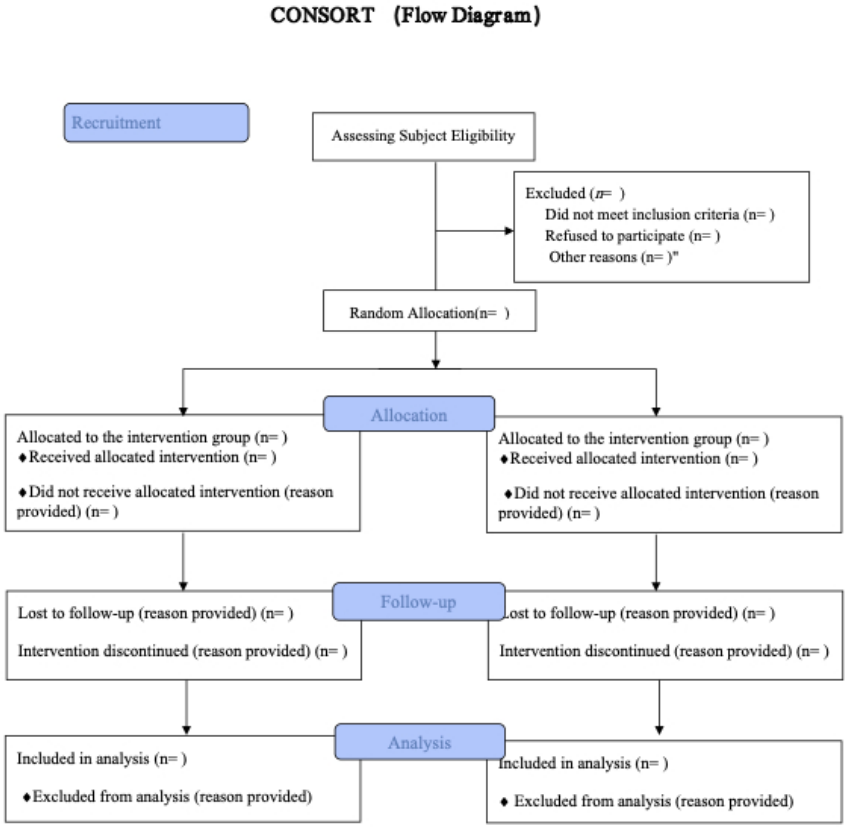

Figure 1: Diagram of the flow of the study

215x279mm (72 x 72 DPI)

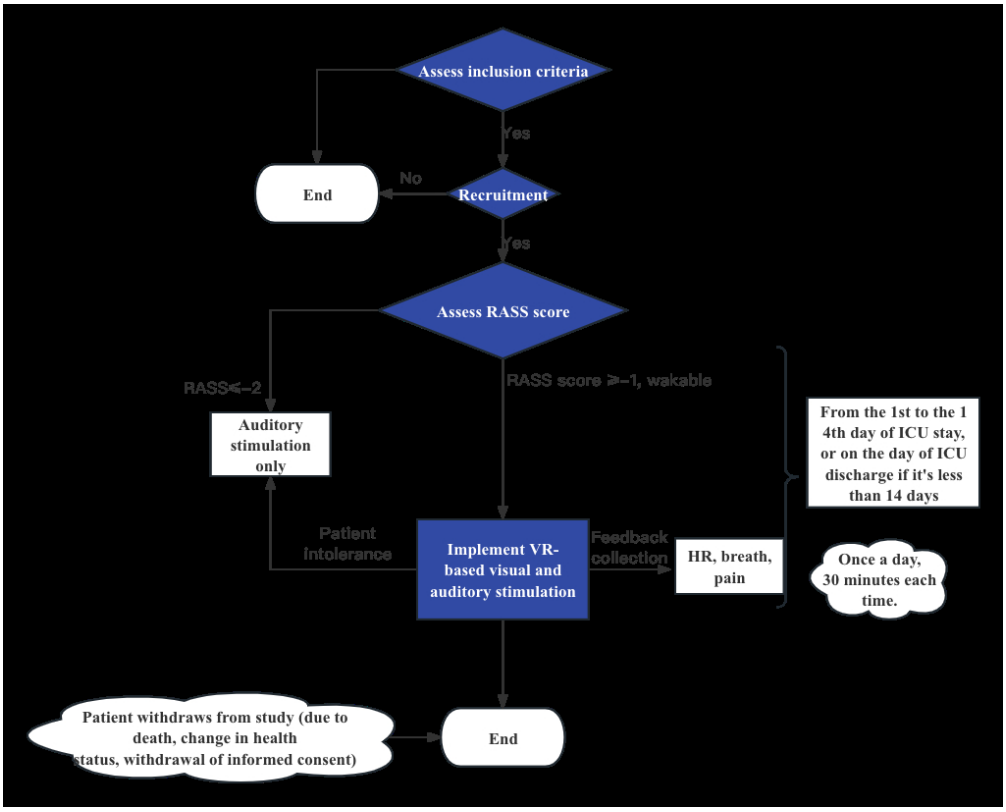

Figure 2: Flowchart of VR-based sensory stimulation implementation

359x288mm (72 x 72 DPI)

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Effectiveness of a Virtual Reality-Based Sensory Stimulation Intervention in Preventing Delirium in Intensive Care Units: A Randomized Controlled Trial Protocol

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Effectiveness of a Virtual Reality-Based Sensory Stimulation Intervention in Preventing Delirium in Intensive Care Units: A Randomized Controlled Trial Protocol

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Contributors LSR, LY, WTX, LD, HMX, and TJF contributed to the study's conception and design. LSR led data management as the principal investigator, while HMX, WTX, and LY developed the study methods and provided supervision. All authors participated in drafting and revising the manuscript. LSR is the guarantor responsible for the integrity of the study. All authors approved the final manuscript and agreed to be accountable for the work.

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Competing interests None declared.

Patient consent for publication Not required.

Ethics approval This protocol was approved by Research Ethics Committee of Shenzhen Hospital of Southern Medical University (NYSZYYEC20230068).

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ABSTRACT

Introduction:

Delirium is a common acute cognitive impairment characterized by confusion, disorientation, and attention deficits, particularly prevalent in ICU settings. Given its significant impact on patients, caregivers, and healthcare resources, preventing delirium in ICU patients is of paramount importance. This is the first randomized controlled trial (RCT) designed to evaluate the effects of a Virtual Reality-based sensory stimulation intervention on preventing delirium in intensive care unit (ICU) patients.

Methods and Analysis:

We employed a paired randomization method to match eligible participants based on a validated delirium risk scoring model for ICU patients. The study will commence in September 2024 and conclude in June 2026. A consecutive sample of 324 ICU patients admitted to the study setting will be recruited. Eligible participants will be randomly allocated to receive either Virtual Reality-based sensory stimulation in addition to usual care or usual care alone. The Virtual Reality-based sensory stimulation intervention will last for up to fourteen days, with all interventions administered by a research team. We define delirium-free days over a 14-day period as the primary outcome. The secondary outcomes will include delirium incidence, duration, and severity, patients' psychological well-being (post-traumatic stress disorder, sleep quality, and ICU memory), patients' clinical outcomes, and other outcomes (quality of life, independence, and cognitive function). Data will be collected at baseline, post-intervention, and six months post-intervention. Two independent t-tests or Wilcoxon-Mann-Whitney tests will be utilized for continuous variables, while chi-square or Fisher's exact tests will be employed for categorical variables. The analysis will

adhere to both the intention-to-treat and per protocol principles. Additionally, mixed-effects models and subgroup analysis will be planned.

Ethics and dissemination This protocol was approved by Research Ethics Committee of Shenzhen Hospital of Southern Medical University (NYSZYYEC20230068). All participants or their family caregivers will provide written informed consent. Results will be disseminated through scientific publications, and presentations at local and international conferences.

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Word counts: 232

Keywords: Critical care; Delirium, Virtual Reality, Sensory stimulation

Article Summary

Strengths and limitations of this study

► This study evaluates a Virtual Reality-based sensory stimulation for preventing delirium and improving patients' psychological well-being (specifically post-traumatic stress disorder, sleep quality, and ICU memory), patients' clinical outcomes (including ICU length of stay), and other outcomes (such as quality of life, independence, and cognitive function).

►This study utilizes a rigorous randomized controlled trial design, incorporating a Virtual Reality-based sensory stimulation intervention for preventing delirium in ICUs. The methodological rigor of this design enhances the reliability and validity of our findings, providing valuable insights into the effectiveness of such interventions in clinical settings.

►Due to the nature of the intervention, blinding was only possible for the outcome assessors, while blinding for the participants and those delivering the intervention was not feasible.

INTRODUCTION

Delirium is a common acute state of cognitive confusion. Intensive Care Unit (ICU) delirium is highly prevalent, with an incidence ranging from 31%[1] to 56%[2], and it can be as high as 81%[3] in ICU patients undergoing mechanical ventilation. A preliminary analysis of data from 375 patients admitted to the ICU for more than 24 hours revealed an occurrence rate of 44% for ICU delirium[4]. Moreover, delirious ICU patients had 1.33 times longer ICU stays and a 9.57-fold increase in mortality compared to non-delirious ICU patients[5]. ICU patients who experience delirium may suffer from post-traumatic stress disorder, anxiety, depression, and cognitive impairment for up to two years[6].

Non-pharmacological preventive measures aim to reduce one or more modifiable risk factors for ICU delirium[7]. Previous research identified sensory stimulation as a key and effective non-pharmacological intervention in preventing ICU delirium[8,9]. Sensory stimulation involves activating one or more senses[10], with visual and auditory stimuli being particularly effective for ICU patients[11]. To further investigate the effectiveness of sensory stimulation in preventing ICU delirium, the research team conducted an initial study to assess the implementation of sensory stimulation on preventing delirium in ICU and subsequently developed a sensory stimulation intervention plan[12,13]. This plan involved daily sessions of 30 minutes each for seven days, including visual stimuli (displaying personal or family photos) and auditory stimuli (playing recordings of family members). The results of the study showed that sensory stimulation reduced the duration and severity of ICU delirium but did not significantly decrease the incidence of ICU delirium[8,9]. The limited effectiveness of sensory stimulation may be attributed to the narrow range of stimuli, insufficient stimulus intensity, and inadequate dosing and implementation methods[9].

In contrast, Virtual Reality (VR) technology, characterized by its three-dimensional and highly immersive qualities, has the potential to provide more effective sensory stimulation by immersing participants in three-dimensional dynamic environments[14]. International researches [15–17] suggest that VR offers significant advantages in sensory stimulation and could be a promising approach for preventing ICU delirium. However, it is important to note that studies on the use of VR in this context are still in the feasibility testing stage. The DREAMS project at the University of Florida in the United States investigated the effectiveness of VR and found that 95.6% of participants found it very comfortable, 51.9% reported improved sleep quality, and 81.5% experienced reduced pain[16]. This team further conducted a study with 46 ICU patients, implementing a seven-day VR intervention, which resulted in reduced stress, pain, anxiety, and improved cognitive function and attention in the participants[17]. Additionally, Jawed and colleagues conducted a preliminary trial that showed VR could alleviate anxiety in ICU patients[15]. However, since those studies were in the feasibility testing stage, they were unable to measure the effects on reducing ICU delirium.

The stress recovery theory and attention restoration theory explain the principles behind preventing ICU delirium using VR-based sensory stimulation[18,19]. The stress recovery theory suggests that natural environments support positive changes in emotional states and psychophysiological recovery, primarily by relaxing the parasympathetic nervous system [19]. In stressful ICU environments, cognitive and attentional resources can become fatigued, which is especially crucial for critically ill patients facing stressors. The cognitive demands and overstimulation in the ICU environment contribute to mental fatigue and stress responses[19]. On the other hand, the attention restoration theory suggests that exposure to natural environments requires fewer cognitive resources and promotes a sense of disengagement from stressors,

allowing attention to rest and recover[18]. Therefore, VR-based visual and auditory stimuli, by immersing patients in relaxing VR environments, may provide a protective effect against environmental stress and support the recovery of physiological, emotional, and attentional functions, thereby helping to prevent delirium. Chirico and colleagues further elucidated the mechanisms of VR-based sensory stimulation in delirium prevention: exposure to VR-based natural environments can trigger a specific psychophysiological pattern activated by the parasympathetic nervous system, leading to intense emotional reactions[20]. Emotion responses increase with higher levels of immersion, which can be utilized to alleviate symptoms like anxiety, pain, and fear, effectively reducing patient stress, improving sleep quality, and consequently reducing the incidence of delirium[20].

Aim and hypothesis

This study aims to evaluate the effects of evaluates a Virtual Reality-based sensory stimulation on preventing delirium, and improving patients' psychological (post-traumatic stress disorder, sleep quality, ICU memory), patients' clinical (ICU length of stay) and other outcomes (quality of life, independence and cognitive function). And the comparator in our study is 'usual care,' representing the standard treatment or practices typically provided in similar clinical settings. It is hypothesised that at patients' fourteenth day of ICU hospitalisation or the day of discharge (if the ICU stay is less than 14 days), will experience the following improvements compared with those receiving usual care.

1. ICU patients receiving the sensory stimulation intervention will have:
    a. A reduction in incidence, duration and severity of delirium.
    b. An improvement in their post-traumatic stress disorder.
    c. An improvement of factual memories.

d. A shorter length of ICU stay.

e. An improvement in quality of life, independence and cognitive function.

At six months after completing the intervention, compared to those receiving usual care, ICU patients undergoing the VR-based sensory stimulation intervention will experience an improvement in quality of life, independence, and cognitive function.

METHODS AND ANALYSIS

Design

A multi-center assessor-blinded two-arm parallel group RCT will be conducted.

Setting

Participants will be recruited from general ICUs of Shenzhen Hospital of Southern Medical University and Shenzhen Hospital of Beijing University, two comprehensive tertiary A -level hospitals in Shenzhen, Guangdong province, Mainland China. Tertiary A-level hospital provides specialist tertiary care in a large hospital after a referral from primary and secondary care[21].

Participants

All ICU patients admitted to the study setting will be recruited if they are/have: (1) aged 18 years or older, (2) first-time admission to the ICU, and (3) a Richmond Agitation-Sedation Scale (RASS) score of ≥-3[22] . Patients will be excluded if they have: (1) been diagnosed with dementia, delirium or acute psychiatric illness at admission, (2) been diagnosed with end-stage cancer, (3) severe hearing impairment and cannot be corrected by hearing aids and (4) been admitted to ICU with radioactive material.

Sample size determination

Sample size calculation for the difference test in delirium incidence between the experimental and control groups was performed using G* Power 3.4. Based on a prior study,

delirium incidence after sensory stimulation was 13%, while it was 25% in the standard care group, yielding an odds ratio of 0.57[8]. For G* Power's two-sample proportion (z-test) calculation, with a significance level set at $\alpha = 0.05$ and a desired test power of Power = 0.8, the required sample size was determined to be 259 participants. Additionally, to account for factors such as patient mortality and loss to follow-up in the ICU, and considering a 20% dropout rate, this study intends to recruit a total of 324 participants, with 162 participants in each group.

Randomisation and allocation concealment

We employed a simple randomization method by generating random numbers through the randomization.com website. Based on these generated numbers, participants were then randomly assigned to either the intervention or control group. To ensure allocation concealment, consecutively numbered, sealed, and opaque envelopes will be utilized. This process will be conducted by a research assistant who will have no further involvement in the study after participant enrollment.

Blinding

Owing to the nature of the intervention, the researchers responsible for delivering the intervention will be aware of the group assignment. However, the outcome assessors will remain blinded to the group allocation and will not participate in data analysis or result reporting.

Intervention

Participants allocated to the intervention group will receive a VR-based sensory stimulation intervention plus usual care. This intervention is designed to provide VR-based visual and auditory stimulation to ICU patients, with additional support from family caregivers. The intervention will be administered by researchers who are trained ICU nurses. It will commence upon the patient's admission and continue until the fourteenth day of their ICU hospitalization or

the day of discharge if their stay is less than 14 days. Each day, a 30-minute session will be conducted [23–25].

The investigator will provide a delirium knowledge leaflet and a sample reorientation message to family caregivers in the intervention group. The investigator will spend 30 minutes explaining the contents to family caregivers during their first meeting. Family caregivers will be asked to prepare the family photographs, family video or recording at their earliest convenience. The leaflet contains information about the definition, prevalence and risk factors of delirium, along with practical steps family caregivers can take to support the patients. These steps include engaging in simple conversations, reminding patients of the current time, date, and location, providing glasses or hearing aids when necessary, decorating patient beds with family photographs, and discussing familiar topics. The reorientation messages serve to help patients understand their surroundings and offer encouragement. Each segment of the message requires two minutes for recording, following the sample message. The leaflet was designed by the investigator, and the sample reorientation message was adapted from a previous study[25]. Both the leaflet and the sample orientation message were reviewed by a committee comprising three ICU nurse specialists, two nurse academics, one physician and two family caregivers.

Each daily session will commence at the earliest available daytime hour, typically between 12:00 and 16:00, following the completion of family recordings. During the pre-bedside phase, the investigator will gather family photographs, recordings, and videos, either digitally recorded or retrieved from previous family collections stored on electronic devices. Subsequently, the investigator will spend 30 minutes with each patient in the intervention group, tailoring the intervention based on the patient's ability to engage with auditory or visual stimulation (**Figure 1**). Notably, the intervention will be discontinued for trial participants under conditions such as participant requests or fluctuations in disease status.

Implementation Content: The intervention consists of the following stages: ① Guidance Stage (2 minutes): Introducing the content and purpose of the VR scenes to be played in the next 30 minutes; ② Relaxation Stage (5 minutes): Selecting natural scenery VR scenes accompanied by soothing background music to help patients relax; ③ Family and Friends Support Stage (18 minutes): Playing VR scene videos provided by family and friends, selecting happy moments and conveying family wishes and blessings; ④ Feedback Stage (5 minutes): Guiding patients to provide feedback and collecting relevant parameters, such as heart rate, respiration, pain, etc.

Control group

Participants in the control group will receive the usual care, consistent with their existing or planned treatment routines. Registered ICU nurses will administer the same nursing care, which includes, but is not limited to, sedation, analgesia, spontaneous breathing trials, indwelling catheter management, feeding, and bowel care.

Outcome and outcome measures

The research will measure the following outcomes. See **Table 1**.

Table 1 Outcomes and time schedules for data collection

Outcome Measures	Data Collection Time Points							Endpoint
	Day1	Day2	Day3	..	..	..	Day14 / Discharge	6 Months Post-Discharge
Delirium Score (CAM-ICU)	X	X	X	..	..	..	X	
Sedation Score (RASS)	X	X	X	..	..	..	X	
Pain Score (NRS)	X	X	X	..	..	..	X	
Pain Score (BPAT)	X	X	X	..	..	..	X	
Sleep (RCSQ)								

	X	X	X	..	..	..	X	
Post-traumatic stress disorder (PCL)							X	
ICU Memory (ICUMT)							X	
Patient Clinical Outcomes							X	
Quality of Life Score (EuroQol)	X						X	X
Independence Function (motor-FIM)	X						X	X
Cognitive function (cognitive-FIM)	X						X	X

Note: CAM-ICU, Confusion Assessment Methods for Intensive Care Units; RASS, Richmond Agitation-Sedation Scale; NRS, numerical rating scale; BPAT, behavior pain assessment tool; RCSQ, Richards-Campbell Sleep Questionnaire; PCL, Posttraumatic Stress Disorder Checklist; ICUMT, Intensive Care Unit Memory Tool; EuroQol, European Health Index; FIM, Functional Independence Measure;

Primary outcomes

Delirium-free days

Our primary outcome will be delirium-free days over a 14-day period, with delirium assessed using the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU) flow sheet. The CAM-ICU is comprised of four features, namely fluctuation of mental status, inattention, altered level of consciousness, and disorganised thinking. CAM-ICU was commonly adopted in ICU settings to measure delirium and was reported to have good interrater reliability (overall kappa coefficient = 0.71)[26].

Secondary outcomes

Delirium incidence, duration and severity

Delirium incidence refers to the number of patients exhibiting delirium. Delirium duration is calculated from the initial delirium diagnosis to the last assessment indicating the absence of delirium, based on CAM-ICU evaluations conducted every eight hours during the patient's stay.

Delirium duration will be measured for each shift and summarized in days. Delirium Severity will be measured by CAM-ICU-7 Delirium Severity Scale, which is a 7-point rating scale derived from the CAM-ICU and Richmond Agitation-Sedation Scale (RASS) assessments. The final CAM-ICU-7 score ranges from 0-7 with 7 being most severe. CAM-ICU-7 scores are further categorised as 0-2: no delirium, 3-5: mild to moderate delirium, and 6-7: severe delirium. CAM-ICU-7 showed a high internal consistency (Cronbach's α = 0.85) and good correlation with Delirium Rating Scale-Revised - 98 (DRS-R-98) (correlation coefficient = 0.64)[27]. The highest CAM-ICU-7 score recorded over the 14-day period will represent delirium severity.

RCSQ

The Richards-Campbell Sleep Questionnaire (RCSQ) is employed to assess the sleep quality of ICU patients. Originally developed for evaluating sleep in critically ill patients, this questionnaire is designed to capture various aspects of sleep during the ICU stay. The scale evaluates perceptions of sleep depth, sleep onset latency, number of awakenings, time spent awake, and overall sleep quality. The content validity of the Chinese version of the RCSQ questionnaire is 0.840, and the Cronbach's α coefficient is 0.874.

PTSD

The 17-item PTSD Checklist (PCL) correspond to the DSM-III-R symptoms of PTSD and serves as a self-report scale for assessing PTSD[28,29]. Patients will be asked to rate their agreement with each item on a scale from one (not at all) to five (extremely). PTSD-symptoms are categorized into re-experiencing (flashback, nightmare, emotional cue reactivity, and physical cue reactivity), avoidance and emotional numbing (avoidance of thoughts and reminders, amnesia, loss of interest, detachment, restricted affect, and foreshortened future), and hyperarousal (irritability/anger, sleep disturbance, difficulty concentrating, hypervigilance, exaggerated startle response). The total score ranges from 17 to 85[30].

A previous study confirmed the good reliability and validity of the PCL, including test-retest reliability of 0.96, internal consistency reliability of 0.94, and predictive validity of 0.64[31]. High correlations with the Symptom Checklist-90 further confirm its reliability and validity[32].

ICU memory

The ICU-Memory Tool (ICU-M) will be used to measure ICU patients' ICU experience[33]. This tool includes 14 questions (five open-ended questions and nine closed-ended questions), and is primarily divided into three parts: memories before admission to the ICU; memories during the ICU stay and memories after transferring out of the ICU. Memories during the ICU stay are categorized into three subscales: factual memories (lights, alarms, voices, families, faces, breathing tube, suctioning, darkness, clock, tube in your mouth, and wound care), memories of feelings (discomfort, confusion, sadness, anxiety/fear, panic, and pain), and memories of delusions (feeling that people were trying to hurt you, hallucinations, nightmares, dreams). The total number of memories in each of the three subscales will be summed. The Chinese version of ICU-M has a Cronbach's α coefficient of 0.823 and a scale-level content validity index of 0.946, confirming its good reliability and validity[34].

Patients' clinical outcomes

Medical outcomes will be extracted by the outcome assessor from the electronic health care system upon participants' discharge. This information includes: (a) ICU length of stay: the total number of days a patient stays in ICU; (b) 30-day mortality: the total death cases among all eligible cases at 30 days after admission to ICU; (c) duration of mechanical ventilation: the registered time in hours that the patients are on the mechanical ventilator; (d) the duration of use of physical restraint: the recorded time in hours that the patients are receiving physical restraint;

(e) sedation use: the documented total amount and average doses (mg/ per day) of sedation by using the conversion measurement of the same quantity of dexmedetomidine. (f) analgesics use: the documented total amount and average doses (mg/ per day) of analgesics using the conversion measurement of the same quantity of propofol. (g) self-extubation: the documented amount of self-extubation cases; (h) ICU acquired infection: the documented amount of self-acquired infection cases.

Quality of life

The EuroQol- 5 Dimension (EQ-5D) will be used to assess the participants' quality of life. It assigns a grade on a scale ranging from 0 (representing the worst possible health status) to 100 (representing the best possible health status) based on one question for each of the five dimensions, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression[35].

Independence and cognitive function

FIM (Functional Independence Measure) will be used to measure both the independence and cognitive function. The FIM is comprised of 18 items, which are grouped into two subscales: motor and cognition. The motor items are adapted from the Barthel Index and are collectively known as the Motor-FIM. These items includes: Eating, Grooming, Bathing, Dressing (upper body), Dressing (lower body), Toileting, Bladder management, Bowel management, Transfers (bed/chair/wheelchair), Transfers (toilet), Transfers (bath/shower), Walk/wheelchair, and Stairs. The cognition subscale, known as the Cognitive-FIM, includes the following items: Comprehension, Expression, Social interaction, Problem solving, and Memory. Each item is scored on a 7-point ordinal scale, ranging from a score of 1 to 7. A higher score indicates greater independence in performing the task associated with that item. The

Inter-Rater Reliability of FIM has been established with acceptable psychometric performance, with Intraclass corelation coefficients ranging from 0.86 to 0.88. Concurrent validity with the Barthel Index (ICC > 0.83) have demonstrated strong construct validity between items on Barthel Index and items on the FIM the measure functional limitations [36].

Sociodemographic and clinical information

Sociodemographic and clinical information including ICU patients and family caregivers' age, gender, educational level, marital status, occupation, the relationship between ICU patients and family caregivers, and the health history of ICU patients will be collected.

Data collection

Two research assistants, both trained consistently, will commence by explaining the study and obtaining written informed consent from the participants. Subsequently, an ICU nurse with a master's degree and a postgraduate student specializing in nursing will gather patients' demographic data from their medical records and collect information on their quality of life, independence, and cognitive function prior to admission to the ICU from the participants' family caregivers. The nurses in charge of the study ICU will assess the CAM-ICU, RASS, RCSQ during daily routine. On the fourteenth day of a patient's ICU hospitalization, or upon discharge if the ICU stay is less than 14 days, the research assistant will collect data on secondary measures (PTSD, ICU memory), clinical outcomes, independence, and cognitive function. Additionally, quality of life, independence, and cognitive function will be assessed via a phone call by the research assistant six months after the completion of the intervention. Notably,
Two research centers each have two research assistants dedicated to obtaining informed consent and collecting data, respectively.

Data management

Each patient has a case report form (CRF) for data collection, initially documented on paper. Following this, the data from the CRFs are transferred to Excel spreadsheets on computers. Access to the Excel files will be restricted through password protection. Only authorized personnel participating in the study will have access to these files. All data entry and manipulation activities will be logged and tracked to maintain transparency and accountability. To identify and rectify errors, such as missing values, outliers, and typos, data cleaning strategies will be employed[37]. Several methods will be employed to detect errors and minimise the impacts on the accuracy of results. Firstly, the original dataset (in Excel) will be manually checked to identify data error. Secondly, statistical graphical explorations including box plots, histograms and scatter plots, along with descriptive statistics such as mean, frequency, and percentage, will be used. Through this process, data errors, including typos, outliers, and violations of integrity constraints, will be corrected.

Data analysis

This study will utilize R4.3.2 software for data analysis, with statistical analysis led by two master's degree-holding research personnel. All statistical tests will be two-tailed, with the significance level set at 0.05. To assess the normal distribution of continuous variables, skewness, kurtosis, Q-Q plots, and histograms will be examined. Variables with skewness and kurtosis values within the range of -2.0 to 2.0 will be considered to have a normal distribution. For normally distributed continuous variables, the study will describe them using the mean ± standard deviation (Mean ± SD). For variables that do not meet the normal distribution criteria, the study will describe them using the median (interquartile range, IQR). Categorical variables will be described using frequency (proportion). If the assumptions for hypothesis testing of

continuous variables are met, independent two-sample t-tests will be used to compare differences between different groups. Otherwise, the Wilcoxon-Mann-Whitney will be employed. For categorical variables, chi-square tests and Fisher's exact tests will be used to compare differences between different groups. Additionally, missing values will be imputed using multiple imputation methods. The study will follow the intention-to-treat (ITT) and per-protocol (PP) principle for analysis. After imputing missing data using multiple imputation methods, the study will perform ITT and PP analysis and report relevant uncertainty indicators, such as confidence intervals and standard errors, in the results. This study will employ mixed-effects models for outcomes with repeated measurements. These models, also known as multilevel or hierarchical models, are effective for analyzing data with a hierarchical structure, such as repeated measurements. Fixed effects will estimate population-level relationships between predictors and outcomes. Our study will include predictors like APACHE-II score, age, admission category, and use of sedatives and analgesics as fixed explanatory variables. Subgroup analyses based on age, gender, and length of ICU stay will be conducted.

DISCUSSION

This study evaluates a Virtual Reality-based sensory stimulation for preventing delirium and improving patients' psychological well-being (specifically post-traumatic stress disorder, sleep quality, and ICU memory), patients' clinical outcomes (including ICU length of stay), and other outcomes (such as quality of life, independence, and cognitive function). It employs a rigorous randomized controlled trial design, incorporating a Virtual Reality-based sensory stimulation intervention within ICUs, which enhances the reliability and validity of findings. The methodological rigor of this design provides valuable insights into the effectiveness of such interventions in clinical settings. Previously, our primary outcome included both the incidence

duration and severity of delirium. However, considering the recommendation to focus on a single primary outcome, we have designated delirium-free days as the primary outcome. Consequently, we have classified delirium duration and severity as secondary outcomes, and this update has been reflected in the trial registry.

In our study, our primary focus is on preventing delirium. However, if delirium does occur, physicians may prescribe antipsychotic medications. We will accurately document whether patients receive these medications and the dosage administered. Furthermore, we will maintain detailed records of the dosage of sedatives and analgesics administered to patients throughout the study. Additionally, in the intervention, family caregivers are involved through a "sample reorientation message," which refers to a written communication provided to help them understand and navigate changes in care, treatment, or environment. We acknowledge that family involvement may influence patient outcomes and could act as a confounding factor in our study. The observed effects may result from a combination of the VR intervention and changes in family behavior. Due to the nature of the intervention, blinding was only possible for the outcome assessors, while blinding for the participants and those delivering the intervention was not feasible.

The study anticipates prompt availability of materials from family members and has contingency plans in place to ensure timely initiation of the VR intervention. However, delays in obtaining materials from family members may occur, potentially impacting the initiation of the VR intervention. Additionally, the use of antipsychotic medications to manage delirium may influence study outcomes, and while their administration will be documented, their effects on study outcomes may not be fully controlled.

ETHICS AND DISSEMINATION

For patients in the Intensive Care Unit ICU, obtaining informed consent can be a complex process due to the patients' health conditions. When possible, and when the patient is capable of understanding and making decisions, we will seek written consent directly from the patient. However, for those who may be too ill to provide consent, we will obtain written consent from their legally authorized representatives, typically family members. We are committed to ensuring that all potential participants, or their designated representatives, are fully informed about the study's objectives and procedures. This includes providing detailed information about the study, its potential risks and benefits, and the voluntary nature of participation.

We are dedicated to upholding the highest ethical standards in disseminating our research findings. Study outcomes will be shared through peer-reviewed publications and presented at academic conferences, ensuring that our work reaches the relevant professional and scientific audiences. We are steadfast in our efforts to safeguard the rights and confidentiality of all participants. To preserve individual privacy, all personal information will be anonymized, and the findings will be communicated in a manner that protects the identities of the participants.

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Competing interests statement

The authors declare that they have no competing interests.

Patient and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Contributors

LSR, LY, WTX, LD, HMX, and TJF contributed to the study's conception and design. LSR led data management as the principal investigator, while HMX, WTX, and LY developed the study methods and provided supervision. All authors participated in drafting and revising the manuscript. LSR is the guarantor responsible for the integrity of the study. All authors approved the final manuscript and agreed to be accountable for the work.

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Figure 1: Flowchart of VR-based sensory stimulation implementation

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