Neuropsychiatric Disease and Treatment

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ORIGINAL RESEARCH

# Frequency and Risk Factors of Subsyndromal Delirium in the Intensive Care Units: A Prospective Cohort Study

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**Background:** Subsyndromal delirium (SSD) is a common neuropsychiatric disorder among the intensive care units (ICU) patients. SSD is characterized by the presence of delirium symptoms but it does not meet the diagnostic criteria of delirium, resulting in poor patient prognosis.

**Objective:** The aim of this study was to explore the prevalence and risk factors for SSD among adult patients admitted to the ICU of XXX hospital in Southwest China.

**Methods:** The study participants comprised 309 patients referred to the ICU in XXX hospital between 10th August 2021 and 5th June 2022. Demographic information, medical history, and other patient information were recorded. ICDSC assessment, physical examination and laboratory tests were performed on enrolled patients. Cognitive evaluation was conducted using the MMSE method.

**Results:** The results showed that out the 309 patients, 99 had possible SSD (prevalence of 32.0%), with 55 SSD1 cases (ICDSC score of 1, 17.8% prevalence), 29 SSD2 cases (ICDSC score of 2, 9.4% prevalence) and 15 SSD3 cases (ICDSC score of 3, 4.9% prevalence). Previous history of mental illness (OR, 3.741; 95% CI, 1.136–12.324; P <0.05), auxiliary ventilation (OR, 3.364; 95% CI, 1.448–7.813; P <0.01), hemodialysis (OR, 11.369; 95% CI, 1.245–103.840; P <0.05), MMSE score (OR, 0.845; 95% CI, 0.789–0.904; P <0.001) and a temperature ≥ 37.5 °C (OR, 3.686; 95% CI, 1.404–9.732; P <0.01) were independent risk factors for occurrence of SSD among ICU patients.

**Conclusion:** Approximately one-third of the patients in the intensive care unit had high risk of SSD. Nursing staff should pay attention to management of the high-risk patients to prevent SSD from progressing delirium to improve patient prognosis.

**Keywords:** intensive care units, ICU, prevalence, risk factors, subsyndromal delirium

## Introduction

Delirium is an acute cognitive impairment syndrome characterized by confusion, blurred consciousness and fluctuating mental status. It is highly common among the intensive care units (ICU) patients.[1,2] Occurrence of delirium is an independent predictor of poor clinical outcome. It can ultimately lead to long-term cognitive impairment and persistence of a dementia state.[3,4] Delirium is currently a major public health concern and research in the field of critical care medicine has been conducted to explore pathogenesis and possible risk factors. The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V)[5] and the International Classification of Diseases 11th Revision (ICD-11)[6] are the main diagnostic criteria for delirium and both require presence of multiple cognitive symptoms. Studies report that some patients only show one or a few of the symptoms in the diagnostic criteria of delirium, but do not meet the diagnostic criteria of delirium. This phenomenon is referred as subsyndromal delirium (SSD)[7] and is a type of neurocognitive disorders.[8]

Received: 3 February 2023
Accepted: 20 April 2023
Published: 28 April 2023



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SSD was reported by the Guainerio scholars in 1517. "A pre-delirium period can be recognized and can progress to incomplete delirium syndrome". In recent years, scholars have come up with different views on the definition of SSD.[9] Levkoff previously reported that SSD is distinct from cognitive and behavioral abnormalities.[7] A study conducted in Germany reported that patients with subdelirium may have one or more incomplete delirium syndromes.[10] Currently, SSD does not have a standardized definition, even in the DSM-V guidelines, which only refers to it as a "subdelirium syndrome" but a clear and uniform diagnostic criteria has not been proposed.[5] In 2013, the American College of Critical Care Medicine published the Clinical Practice Guidelines for Pain, Agitation, and Delirium in Adult ICU Patients, which defines delirium as a syndrome characterized by an acute onset of cerebral impairment with a change or fluctuation in mental status from basal, inattention, or disorganization of thinking, or a change in level of consciousness as the main clinical manifestations.[11] SSD was defined as presence of some of the symptoms of delirium.

Recent studies report that the cognitive state of SSD is intermediate between delirium and normal cognition, with high clinical morbidity and a negative impact on clinical outcomes.[12,13] Yamada et al[14] evaluated 380 patients in the ICU and observed that subdelirium syndrome occurred in approximately 33.9% of the patients, with 9.5% of the patients progressing from subdelirium to delirium. The progression of subdelirium to delirium resulted in increased duration of mechanical ventilation and hospitalization, increased incidence of bed falls, extubation, stress injuries and increased hospital costs. Available epidemiological data on SSD is mainly on elderly patients and postoperative cardiac patients.

Previous studies report a prevalence of 6% to 75.6% in elderly patients with SSD and a combined prevalence of 36.4%.[15] The incidence of SSD in post-operative cardiac patients is 34%, the incidence of delirium in this group is 12%, and delirium occurs in approximately 2% of SSD patients.[16] A previous study reported 31% SSD incidence in non-cardiac post-operative patients.[13] A systematic evaluation and meta of the incidence and the risk factors of SSD in ICU patients conducted by Li Zhen et al showed that SSD incidence was 36.9%, but only one article from the Chinese region was included in the analysis. The subgroup analysis in the study showed that the incidence varied between geographic regions.[17] Currently, only a few studies have been conducted on the incidence and risk factors of SSD in ICU patients in China. The incidence of SSD in central ICU patients may be influenced by the specificity of their environment and condition, and the risk factors for SSD may also be specific.

Therefore, the aim of this study was to evaluate the incidence and risk factors of SSD in ICU patients admitted to a tertiary care hospital in southwest China. The study sought to identify specific risk factors and provide a scientific basis for the clinical identification of high-risk SSD groups in ICU. The findings will provide a basis for the implementation of effective preventive and treatment measures.

# Materials and Methods

## Study Design

A single-center, prospective cohort study design was used in the present study.

## Participants

Adult patients admitted for more than 12 hours to the central ICU of the Second Affiliated Hospital in Chongqing, Southwest China, between August 10, 2021, and June 5, 2022 were recruited to this study. The facility is a 2580-bed tertiary referral hospital that serves a population of 10 million people. The central ICU has 31 beds. Patients under the age of 18; patients diagnosed with delirium or SSD during admission; subjects in a deep coma, as determined using the Glasgow Coma Scale[18] (GCS; Score less than 8 points) and patients who were deeply sedated, as determined with the Richmond Agitation Sedation Scale[19] (RASS; scores −4 and −5); and subjects with alcohol withdrawal reactions were excluded from the study.

## Measurements

All nurses in the intensive care unit underwent a uniform SSD assessment training and had passed the assessment training before they were allowed to conduct clinical assessments. Patients were assessed immediately after admission by the nurse in charge using the Intensive Care Delirium Screening Checklist (ICDSC) and then daily at a fixed time point

(8:00 to 9:00). Patients who exhibited fluctuations in condition, changes in cognitive level or level of consciousness, or were under analgesic and sedative medication, were assessed and recorded at all times until the patient was transferred from the ICU, or delirium or death occurred. The nurse consulted the attending physician or a light psychiatrist in case of doubts about the assessment. The patient's condition was recorded in detail on a record sheet for patients who were not suitable for assessment.

The ICDSC method is used to assess the level of consciousness, inattention, disorientation, hallucinations, psychomotor, language or mood disorders, sleep disturbances and symptom fluctuations. Patients are diagnosed with delirium when they exhibit deviations in at least four of the eight items in the ICDSC assessment. Patients with a score between 1 and 3 for the items are diagnosed with subclinical delirium. The ICDSC assessment has 99% inter-observer reliability and 64% specificity for caregivers and physicians.[20]

Social and medical characteristics of the patients and treatment details during hospitalization were obtained from electronic medical records. Comorbidity was evaluated using the Charlson Comorbidity Index (CCI) provided by the International Statistical Classification of Diseases and Related Health Problems, 10th Edition. Age was excluded from the determination of the CCI and evaluated independently. Cognitive level during admission was assessed based on clinical experience and the Brief Mental Status Examination Scale (MMSE), which was developed by Nasreddine et al.[21] The MMSE comprises 8 cognitive domains, namely visuospatial and executive functions, naming, memory, attention, language, abstraction, delayed recall and orientation, and has a total of 12 items and a total score of 30.[22] The total score is increased by 1 if the patient has ≤12 years of literacy. Normal cognitive function has a score of ≥23 and the score of cognitive impairment is <23.[23] Sleep quality was evaluated using the Richards-Campbell Sleep Questionnaire (RCSQ). The RCSQ scale has five items for evaluating sleep depth, sleep latency, re-entry, nocturnal awakenings and sleep quality. The sixth item is not part of the original RCSQ scale but can be used to assess the patient's subjective perception of noise. Each item is scored on a visual analogue scale of 0–100 mm (l mm =1 point), with a score of 0 indicating the worst sleep quality and 100 indicating the best sleep quality. The total score of the scale was the average of the sum of the scores for the 5 items, with 0–25 indicating poor sleep quality and 76–100 indicating good sleep quality. Higher scores indicated better sleep quality.

## Ethical Procedures

The procedures and rationale for the study were explained to all patients and relatives. Most patients were critically ill at the time of admission to the ICU, so they were not able to provide informed written consent. The Ethics Committee approved proxy consent for all participants by close relatives (where possible) or responsible caregivers due to the non-invasive nature of the study in accordance with the Helsinki Guidelines for Medical Research Involving Human Participants.[24]

## Data Analysis

The sample size was calculated using PASS 2021 software (Version 21.0, NCSS Crop., USA). A previous study reported that the incidence of SSD is approximately 40%.[17] Yamada et al[14] observed that a history of cognitive impairment accounted for approximately 4.73% of SDD incidence when used as an independent risk factor for SSD, with an Odds Ratio value of 13.1. The required sample size was determined as 278 cases with an alpha of 0.05 (two-sided test) and a certainty of 0.8. A total of 309 cases were therefore included in this study considering 10% dropout, which would ensure the scientific validity of the study.

Statistical analysis was performed using SPSS Statistical software for Windows, version 26.0 (Armonk, NY, US: IBM Corp.). Descriptive statistics were used to describe patients with no SSD and patients with SSD using scores of 1, 2, and 3, respectively. The mean was calculated for continuous data and the percentage was determined for binary data for all groups. Independent samples *t*-test was performed to determine the difference in means and Chi-square test was performed for determination of differences for the binary data ($p < 0.05$).

The relationship between SSD and susceptibility factors was evaluated through univariate analysis. Variables significantly associated with SSD based on the univariate analysis were used for binary logistic regression analysis. The final delirium prediction model was fitted using a forward stepwise selection method. The goodness of fit was

determined using the Chi-square test. The patient's last assessment before SSD occurred was used for case group and the highest total score was used for the control group to conduct univariate and regression analyses. A value of $\alpha = 0.05$ was the threshold for statistical significance.

## Results

A total of 539 patients were referred to the central ICU of the Second Affiliated Hospital in Chongqing, China for evaluation and treatment during the study period. Out of the 539 patients, 309 patients were included in the present study (Figure 1). 230 patients were excluded from the study owing to the following reasons: 101 patients were in coma throughout the study period; 56 patients had a RASS score of −4 or −5; 33 patients were admitted to the ICU for less than 12 hours; 10 patients were diagnosed with delirium; 17 patients were less than 18 years old; 8 patients died during the assessment; 3 patients or family members declined to participate; and 2 patients were unable to communicate. The baseline demographic data of the patients included in study are shown in Table 1.

### Prevalence of Subsyndromal Delirium

The results showed that 191 subjects were males (61.8%) and 118 were females (38.2%) out of the 309 patients who underwent diagnostic assessment. The mean age of the patients was 58.35 years. Surgical admissions had the highest number of patients (195/63.1) and patients referred for post-operative reasons were 194/62.8 and patients with emergency admission were 115/37.2. Most of the patients were married (280/90.6) and the highest level of education of the subjects was secondary (146/47.2).

The characteristics of SSD1, SSD2 and SSD3 patients and patients without delirium are presented in Table 1. Patients with high SSD risk were older than those without delirium. SSD patients exhibited an increasing trend in mean age with increase in SSD scores. The results showed that 99 patients had possible SSD (prevalence of 32.0%), with 55 diagnosed with SSD 1 (prevalence of 17.8%), 29 with SSD 2 (prevalence of 9.4%) and 15 with SSD 3 (prevalence of 4.9%).

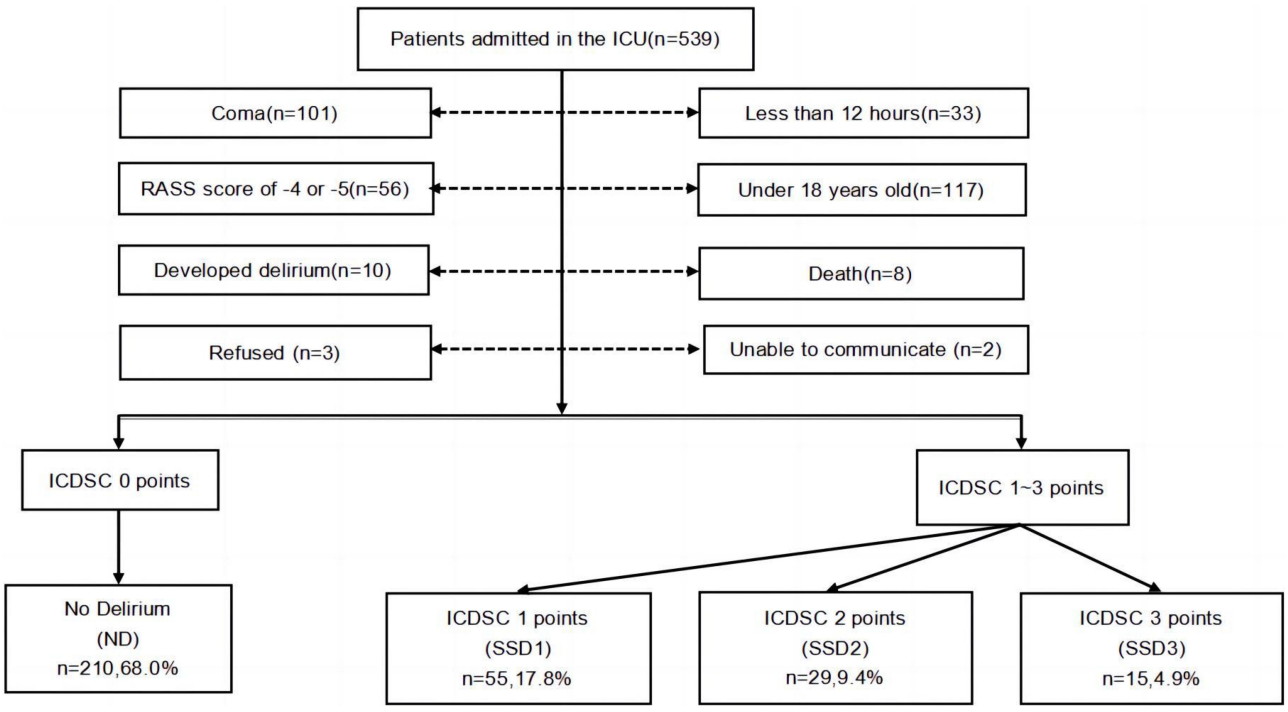


**Figure 1** Diagram of patient flow in the study.
**Abbreviations**: ICDSC, Intensive Care Delirium Screening Checklist; ICU, Intensive Care Unit; ND, Non-delirium; RASS, Richmond Agitation Sedation Scale; SSD, subsyndromal delirium.

**Table 1** Patient Characteristics

| | | ND Group (N=210) | SSD Group (N=99) | | |
|---|---|---|---|---|---|
| | | | SSD=1 | SSD=2 | SSD=3 |
| ***Demographic characteristics*** | | | | | |
| Gender, n(%) | Male | 126(60.00) | 35(35.35) | 21(21.21) | 9(9.09) |
| | Female | 84(40.00) | 20(20.20) | 8(8.08) | 6(6.06) |
| Age, [years, M(SD)] | | 56.79(16.80) | 60.98(15.28) | 62.48(13.56) | 62.60(14.19) |
| Admission Department, n(%) | Surgery | 135(64.29) | 34(34.34) | 16(16.16) | 10(10.10) |
| | Internal Medicine | 57(27.14) | 17(17.17) | 11(11.11) | 4(4.04) |
| | Obstetrics and Gynaecology | 4(1.90) | 1(1.01) | 0 | 0 |
| | Emergency Care | 2(0.95) | 1(1.01) | 0 | 0 |
| | ICU | 12(5.71) | 2(2.02) | 2(2.02) | 1(1.01) |
| BMI [kg/m$^2$, M(SD)] | | 22.76(3.57) | 22.99(3.58) | 23.18(4.45) | 22.98(3.22) |
| Medical insurance, yes(%) | | 187(89.05) | 50(50.51) | 26(26.26) | 13(13.1) |
| Pre-admission living environment, n(%) | Home | 189(90.00) | 48(48.48) | 23(23.23) | 14(14.14) |
| | Nursing care | 10(4.76) | 4(4.04) | 3(3.03) | 1(1.01) |
| | Hospital | 11(5.24) | 3(3.03) | 3(3.03) | 0 |
| Admission mode, n(%) | Emergency admission to ICU | 75(35.71) | 19(19.19) | 14(14.14) | 7(7.07) |
| | Postoperative transfer to ICU | 135(64.29) | 36(36.36) | 15(15.15) | 8(8.08) |
| Marital status, n(%) | Unmarried | 14(6.67) | 4(4.04) | 0 | 1(1.01) |
| | Married | 188(89.52) | 50(50.51) | 28(28.28) | 14(14.14) |
| | Divorce | 2(0.95) | 0 | 1(1.01) | 0 |
| | Widowed | 6(2.86) | 1(1.01) | 0 | 0 |
| Education, n(%) | Illiterate | 14(6.67) | 5(5.05) | 3(3.03) | 4(4.04) |
| | Primary school | 69(32.86) | 17(17.17) | 13(13.13) | 3(3.03) |
| | Middle school | 101(48.10) | 26(26.26) | 13(13.13) | 6(6.06) |
| | College degree or above | 26(12.38) | 7(7.07) | 0 | 2(2.02) |
| ***Medical history*** | | | | | |
| Impaired hearing, yes(%) | | 19(9.05) | 5(5.05) | 4(4.04) | 2(2.02) |
| Impaired vision, yes(%) | | 26(12.38) | 8(8.08) | 4(4.04) | 1(1.01) |
| History of smoking, yes(%) | | 76(36.19) | 19(19.19) | 14(14.14) | 5(5.05) |
| History of drinking, yes(%) | | 53(25.24) | 16(16.16) | 14(14.14) | 5(5.05) |
| History of allergy, yes(%) | | 13(6.19) | 1(1.01) | 2(2.02) | 0 |
| Hypertension, yes(%) | | 50(23.81) | 23(23.23) | 11(11.11) | 7(7.07) |
| Diabetes, yes(%) | | 31(14.76) | 4(4.04) | 10(10.10) | 1(1.00) |
| History of mental illness, yes(%) | | 8(3.81) | 6(6.06) | 5(5.05) | 1(1.01) |
| History of fall, yes(%) | | 35(16.67) | 13(13.13) | 5(5.05) | 3(3.03) |

(*Continued*)

**Table 1** (Continued).

| | | ND Group (N=210) | SSD Group (N=99) | | |
|---|---|---|---|---|---|
| | | | SSD=1 | SSD=2 | SSD=3 |
| History of surgical | | 96(45.71) | 24(24.24) | 13(13.13) | 7(7.07) |
| History of blood transfusion, yes(%) | | 25(11.90) | 5(5.05) | 2(2.02) | 2(2.02) |
| History of antidepressant/ benzodiazepine use, yes(%) | | 16(7.62) | 5(5.05) | 4(4.04) | 1(1.01) |
| ***Modifiable risk factors*** | | | | | |
| Auxiliary ventilation, yes(%) | | 146(69.52) | 46(46.46) | 21(21.21) | 12(12.12) |
| Catheterization, yes(%) | | 168(80.00) | 49(49.49) | 24(24.24) | 13(13.13) |
| Number of catheters≥3 | | 135(64.29) | 40(40.40) | 23(23.23) | 5(5.05) |
| Use of dehydrating agent, yes(%) | | 129(61.43) | 29(29.29) | 18(18.18) | 10(10.10) |
| Hemodialysis, yes(%) | | 11(5.24) | 10(10.10) | 6(6.06) | 3(3.03) |
| Metabolic acidosis, yes(%) | | 21(10.00) | 5(5.05) | 5(5.05) | 3(3.03) |
| Active state, n(%) | Active decubitus | 164(78.10) | 43(43.43) | 20(20.20) | 9(9.09) |
| | Passive decubitus | 45(21.43) | 12(12.12) | 9(9.09) | 6(6.06) |
| | Forced lying position | 1(0.48) | 0 | 0 | 0 |
| Benzodiazepine, yes(%) | | 18(8.57) | 2(2.02) | 6(6.06) | 1(1.01) |
| Steroid drugs, yes(%) | | 46(21.90) | 11(11.11) | 9(9.09) | 4(4.04) |
| Number of medications≥5, yes(%) | | 73(34.76) | 23(23.23) | 19(19.19) | 4(4.04) |
| Constraint, yes(%) | | 82(39.05) | 27(27.27) | 12(12.12) | 8(8.08) |
| Pain, yes(%) | | 126(60.00) | 38(38.38) | 17(17.17) | 12(12.12) |
| Analgesia, yes(%) | | 124(59.05) | 36(36.36) | 21(21.21) | 11(11.11) |
| Calm, yes(%) | | 102(48.57) | 31(31.31) | 17(17.17) | 9(9.09) |
| Transfusion in ICU, yes(%) | | 123(58.57) | 30(30.30) | 14(14.14) | 10(10.10) |
| Use of antibiotics, yes(%) | | 155(73.81) | 43(43.43) | 25(25.25) | 11(11.11) |
| Surgery, yes(%) | | 169(80.48) | 43(43.43) | 19(19.19) | 10(10.10) |
| CRP, n(%) | <5.0 | 64(30.48) | 18(18.18) | 6(6.06) | 4(4.04) |
| | 5.0–200 | 122(58.10) | 32(32.24) | 21(21.21) | 8(8.08) |
| | >200 | 24(11.43) | 5(5.05) | 2(2.02) | 3(3.03) |
| hs-CRP>5.0, yes(%) | | 147(70.00) | 36(36.36) | 23(23.23) | 11(11.11) |
| CCI, M(SD) | | 4.06(3.29) | 3.65(3.00) | 4.31(3.08) | 3.07(1.98) |
| MMSE, M(SD) | | 23.90(4.35) | 21.25(4.08) | 18.10(5.53) | 20.67(4.79) |
| RCSQ, M(SD) | | 62.65(16.76) | 59.55(18.45) | 62.86(13.74) | 62.27(11.99) |
| T≥37.5°C, yes(%) | | 17(8.10) | 8(8.08) | 4(4.04) | 2(2.02) |
| Systolic pressure [mmol/L, M(SD)] | | 126.71(23.94) | 126.20(29.51) | 124.31(24.32) | 127.60(26.81) |
| Diastolic pressure [mmol/L, M(SD)] | | 79.16(15.26) | 79.64(20.17) | 76.97(12.70) | 84.73(20.87) |
| HR, M(SD) | | 93.48(23.63) | 95.20(24.01) | 100.41(26.43) | 99.53(32.41) |

(*Continued*)

**Table 1** (Continued).

| | ND Group (N=210) | SSD Group (N=99) | | |
|---|---|---|---|---|
| | | SSD=1 | SSD=2 | SSD=3 |
| Intake [mL, M(SD)] | 1933.61(1150.98) | 2038.47(1454.86) | 1929.48 (1342.22) | 2161.33 (1101.21) |
| Output [mL, M(SD)] | 1676.77(1094.32) | 1561.80(864.76) | 1339.07(799.36) | 1862.80 (1208.95) |
| ADL, M(SD) | 7.05(13.89) | 4.00(8.02) | 4.14(9.17) | 4.67(13.16) |
| APACHEII, M(SD) | 15.09(6.29) | 17.51(6.27) | 17.14(6.26) | 17.20(7.89) |
| Caprini, M(SD) | 7.74(3.37) | 7.96(4.06) | 8.55(3.71) | 9.00(3.85) |
| PH, M(SD) | 7.38(0.07) | 7.38(0.07) | 7.36(0.10) | 7.38(0.07) |
| PaO2, M(SD) | 130.36(54.11) | 135.85(60.93) | 117.00(44.85) | 103.53(36.60) |
| PaCO2, M(SD) | 37.48(10.44) | 38.49(10.46) | 39.45(10.28) | 38.07(10.10) |
| K, M(SD) | 4.07(0.68) | 3.81(0.61) | 4.07(0.73) | 3.98(0.93) |
| Na, M(SD) | 135.84(4.70) | 136.63(7.86) | 135.76(6.16) | 138.40(4.44) |
| Ca, M(SD) | 1.12(0.10) | 1.10(0.16) | 1.13(0.17) | 1.13(0.12) |
| CL, M(SD) | 106.68(11.24) | 107.25(5.64) | 107.18(6.24) | 108.87(4.39) |
| Blood glucose, M(SD) | 10.70(8.28) | 9.33(2.98) | 10.86(4.97) | 8.77(4.01) |
| RBC [×10^12/L, M(SD)] | 3.60(1.68) | 4.24(5.02) | 3.29(0.76) | 5.88(9.63) |
| HBG [g/L, M(SD)] | 103.26(27.33) | 104.33(30.79) | 96.07(22.74) | 106.13(38.60) |
| HCT [%, M(SD)] | 31.73(10.63) | 31.68(9.33) | 28.72(8.11) | 32.19(11.69) |
| WBC [×10^9/L, M(SD)] | 12.33(11.01) | 12.46(6.21) | 12.29(5.20) | 11.05(6.98) |
| PLT [×10^9/L, M(SD)] | 184.34(109.86) | 194.62(94.40) | 146.77(96.67) | 151.53(105.67) |
| NEUT, [×10^9/L, M(SD)] | 13.50(46.89) | 10.92(6.02) | 13.00(9.91) | 9.68(6.67) |
| Lym [×10^9/L, M(SD)] | 5.82(69.86) | 0.89(0.50) | 0.72(0.35) | 0.81(0.55) |
| Mg [mmol/L, M(SD)] | 2.50(11.66) | 0.88(0.18) | 0.90(0.18) | 0.94(0.13) |
| TP [g/L, M(SD)] | 55.56(12.08) | 56.36(9.82) | 68.65(77.79) | 60.27(11.14) |
| ALB [g/L, M(SD)] | 32.60(6.54) | 35.09(16.94) | 30.03(4.49) | 33.05(6.72) |
| Cr [umol/L, M(SD)] | 102.98(111.47) | 133.47(180.09) | 138.28(137.21) | 146.13(148.81) |
| TBIL [umol/L, M(SD)] | 21.23(24.45) | 36.16(75.03) | 35.18(61.15) | 27.21(18.76) |
| LAC [mmol/L, M(SD)] | 3.49(3.47) | 3.04(1.27) | 3.01(1.16) | 4.28(3.64) |
| PCT [ng/mL, M(SD)] | 6.76(28.66) | 1.68(3.76) | 5.10(15.89) | 22.25(61.70) |
| FIB [g/L, M(SD)] | 3.42(2.47) | 3.32(1.36) | 3.77(1.57) | 3.08(1.36) |

**Abbreviations**: ADL, activities of daily living; APACHE, Acute Physiology and Chronic Health Evaluation; BMI, Body Mass Index; CCI, Charlson Comorbidity Index; Cr, creatinine; CRP, C-reactive protein; FIB, Fibrinogen; HCT, Red blood cell specific volume; HGB, hemoglobin; HR, Heart rate; hs-CRP, hypersensitive C-reactive protein; ICU, Intensive Care Unit; LAC, lactic acid; Lym, leukomonocyte; M, Mean; MFS, Morse Fall Scale; MMSE, Mini-mental State Examination; n, number; NEUT, neutrophil; NRS, Nutrition risk screening; PCT, procalcitonin; PLT, Platelets; RBC, red blood cell count; RCSQ, Richards-Campbell Sleep Questionnaire; SD, Standard Deviation; SSD, Subsyndromal delirium; T, Temperature; TBIL, total bilirubin; TP, Total protein; WBC, leukocyte.

## Risk Factors

Sociodemographic risk factor analysis of enrolled patients showed that age (OR, −2.484; 95% CI, −8.739- −1.013; P<0.05) was a risk factor for SSD. A history of hypertension (OR, 0.442; 95% CI, 0.265–0.737; P<0.01) and a history of

previous mental illness (OR, 0.213; 95% CI, 0.078–0.586; P<0.01) were risk factors for SSD. Analysis of risk factors after admission showed that auxiliary ventilation (OR, 0.552; 95% CI, 0.312–0.977; P<0.05), hemodialysis treatment (OR, 0.233; 95% CI, 0.106–0.511; P<0.001), functional activity status (P<0.05), number of drugs taken during hospitalization ≥5 (OR, 0.614; 95% CI, 0.3377–0.999; P<0.05), MMSE score (OR, 6.668; 95% CI, 2.582–4.743; P<0.001), body temperature > 37.5 °C (OR, 0.431; 95% CI, 0.201–0.921; P<0.05), ADL score (OR, 2.00; 95% CI, 0.044–5.016; P<0.05), APACHEII score (OR, −4.12; 95% CI, −4.469–1.582; P<0.001) and magnesium content (OR, 1.992; 95% CI, 0.016–3.191; P<0.05) were the risk factors of SSD (Table 2).

Univariate logistic regression showed verified the association between the variables and SSD (Table 2). Multivariate analysis showed that the five factors were independently associated with SSD. Multivariate analysis showed that a history

**Table 2** Univariate and Multifactorial Analysis of Susceptibility Factors for SSD

| | ND Group (N=210) | SSD Group (N=99) | Univariate Model | | Multivariate Model | |
|---|---|---|---|---|---|---|
| | | | OR(95% CI) | P | OR(95% CI) | P |
| ***Demographic characteristics*** | | | | | | |
| Gender, n(%) | | | 0.785(0.477,1.291) | 0.340 | | |
| Male | 126(60.0) | 65(65.7) | | | | |
| Female | 84(40.0) | 34(34.3) | | | | |
| Age, [years, M(SD)] | 56.79(16.797) | 61.67(14.512) | −2.484(−8.739,-1.013) | 0.014* | 0.996(0.975,1.017) | 0.717 |
| Admission Department, n(%) | | | | 0.885 | | |
| Surgery | 135(64.3) | 60(66.7) | | | | |
| Internal Medicine | 57.(27.1) | 32(32.3) | | | | |
| Obstetrics and Gynaecology | 4(1.9) | 1(1.0) | | | | |
| Emergency Care | 2(1.0) | 1(1.0) | | | | |
| ICU | 12(5.7) | 5(5.1) | | | | |
| BMI [kg/m$^2$, M(SD)] | 22.76(3.572) | 23.05(3.746) | −0.656(−1.160, 0.580) | 0.513 | | |
| Medical insurance, yes(%) | 187(89.0) | 89(89.9) | 0.914(0.417,2.001) | 0.821 | | |
| Pre-admission living environment, n(%) | | | | 0.476 | | |
| Home | 189(90.0) | 85(85.9) | | | | |
| Nursing care | 10(4.8) | 8(8.1) | | | | |
| Hospital | 11(5.2) | 6(6.1) | | | | |
| Admission mode, n(%) | | | 0.819(0.502,1.339) | 0.426 | | |
| Emergency admission to ICU | 75(35.7) | 40(40.4) | | | | |
| Postoperative transfer to ICU | 135(64.3) | 59(59.6) | | | | |
| Marital status, n(%) | | | | 0.708 | | |
| Unmarried | 14(6.7) | 92(92.9) | | | | |
| Married | 188(89.5) | 5(5.1) | | | | |
| Divorce | 2(1.0) | 1(1.0) | | | | |
| Widowed | 6(2.9) | 1(1.0) | | | | |

(*Continued*)

**Table 2** (Continued).

| | ND Group (N=210) | SSD Group (N=99) | Univariate Model | | Multivariate Model | |
|---|---|---|---|---|---|---|
| | | | OR(95% CI) | P | OR(95% CI) | P |
| Education, n(%) | | | | 0.373 | | |
| Illiterate | 14(6.7) | 12(12.1) | | | | |
| Primary school | 69(32.9) | 33(33.3) | | | | |
| Middle school | 101(48.1) | 45(24.5) | | | | |
| College degree or above | 26(12.4) | 9(9.1) | | | | |
| ***Medical history*** | | | | | | |
| Impaired hearing, yes(%) | 19(9.0) | 11(11.1) | 0.796(0.363,1.744) | 0.568 | | |
| Impaired vision, yes(%) | 26(12.4) | 13(13.1) | 0.935(0.458,1.908) | 0.853 | | |
| History of smoking, yes(%) | 76(36.2) | 38(38.4) | 0.910(0.556,1.491) | 0.709 | | |
| History of drinking, yes(%) | 53(25.2) | 35(35.4) | 0.617(0.368,1.035) | 0.066 | | |
| History of allergy, yes(%) | 13(6.2) | 3(3.0) | 2.112(0.588,7.586) | 0.242 | | |
| Hypertension, yes(%) | 50(23.8) | 41(41.4) | 0.442(0.265,0.737) | 0.002** | 1.484(0.771,2.859) | 0.237 |
| Diabetes, yes(%) | 31(14.8) | 15(15.2) | 0.970(0.497,1.893) | 0.928 | | |
| History of mental illness, yes(%) | 8(3.8) | 12(12.1) | 0.213(0.078,0.586) | 0.001** | 3.741(1.136,12.324) | 0.030* |
| History of fall, yes(%) | 35(16.7) | 21(21.2) | 0.743(0.406,1.358) | 0.333 | | |
| History of surgical, yes(%) | 96(45.7) | 44(44.4) | 1.053(0.651,1.702) | 0.834 | | |
| History of blood transfusion, yes(%) | 25(11.9) | 9(9.1) | 1.351(0.606,3.015) | 0.461 | | |
| History of antidepressant/ benzodiazepine use, yes(%) | 16(7.6) | 10(10.1) | 0.734(0.320,1.682) | 0.463 | | |
| ***Modifiable risk factors*** | | | | | | |
| Auxiliary ventilation, yes(%) | 146(69.5) | 79(79.8) | 0.552(0.312,0.977) | 0.040* | 3.364(1.448,7.813) | 0.005** |
| Catheterization, yes(%) | 168(80.0) | 86(86.9) | 0.605(0.308,1.187) | 0.141 | | |
| Number of catheters≥3, yes(%) | 135(64.3) | 68(68.7) | 0.821(0.493,1.366) | 0.447 | | |
| Use of dehydrating agent, yes(%) | 129(61.4) | 57(57.6) | 1.173(0.722,1.908) | 0.519 | | |
| Hemodialysis, yes(%) | 11(5.2) | 19(19.2) | 0.233(0.106,0.511) | 0.000*** | 11.369(1.245,103.840) | 0.031* |
| Metabolic acidosis, yes(%) | 21(10.0) | 3(13.1) | 0.735(0.352,1.536) | 0.412 | | |
| Active state, n(%) | | | | 0.049* | | |
| Active decubitus | 164(78.1) | 65(65.7) | | | 2.097(0.199,22.104)[a] | 0.538 |
| Passive decubitus | 45(21.4) | 21(21.2) | | | 1.801(0.164,19.720)[a] | 0.164 |
| Forced lying position | 1(0.5) | 13(13.1) | | | | |
| Benzodiazepine, yes(%) | 18(8.6) | 9(9.1) | 0.938(0.405,2.168) | 0.880 | | |
| Steroid drugs, yes(%) | 46(21.9) | 24(24.2) | 0.8877(0.499,1.541) | 0.647 | | |
| Number of medications≥5, yes(%) | 73(34.8) | 46(46.5) | 0.614(0.377,0.999) | 0.049* | 1.677(0.930,3.023) | 0.086 |
| Constraint, yes(%) | 82(39.0) | 47(47.5) | 0.709(0.438,1.148) | 0.161 | | |
| Pain, yes(%) | 126(60.0) | 67(67.7) | 0.716(0.433,1.185) | 0.193 | | |

(*Continued*)

**Table 2** (Continued).

| | ND Group (N=210) | SSD Group (N=99) | Univariate Model | | Multivariate Model | |
|---|---|---|---|---|---|---|
| | | | OR(95% CI) | P | OR(95% CI) | P |
| Analgesia, yes(%) | 124(59.0) | 68(68.7) | 0.657(0.396,1.090) | 0.103 | | |
| Calm, yes(%) | 102(48.6) | 57(57.6) | 0.696(0.430,1.127) | 0.139 | | |
| Transfusion in ICU, yes(%) | 123(58.6) | 54(54.5) | 1.178(0.728,1.907) | 0.504 | | |
| Use of antibiotics, yes(%) | 155(73.8) | 79(79.8) | 0.713(0.400,1.273) | 0.252 | | |
| Surgery, yes(%) | 169(80.5) | 72(72.7) | 1.546(0.884,2.702) | 0.125 | | |
| CCI, M(SD) | 4.06(3.286) | 3.76(2.896) | 0.812 | 0.418 | | |
| MMSE, M(SD) | 23.90(4.353) | 20.24(4.813) | 6.668(2.582,4.743) | 0.000*** | 0.845(0.789,0.904) | 0.000*** |
| RCSQ, M(SD) | 62.65(16.764) | 60.93(16.263) | 0.849(−2.265,5.702) | 0.397 | | |
| T≥37.5°C | 17(8.1) | 15(15.2) | 0.431(0.201,0.921) | 0.027* | 3.686(1.404,9.732) | 0.008** |
| Systolic pressure [mmHg, M(SD)] | 126.71(23.938) | 126.71(23.938) | 0.280(5.167,6.879) | 0.780 | | |
| Diastolic pressure [mmHg, M(SD)] | 79.16(15.256) | 79.63(18.398) | −0.220(−4.670,3.732) | 0.826 | | |
| HR, M(SD) | 93.48(23.627) | 97.38(25.951) | −1.314(19.759,1.944) | 0.190 | | |
| Intake [mL, M(SD)] | 1933.61 (1150.982) | 2025.16 (1363.786) | −0.614(−384.918,201.814) | 0.540 | | |
| Output [mL, M(SD)] | 1676.77 (1094.315) | 1676.77 (1094.315) | 1.062(−114.775,383.994) | 0.289 | | |
| ADL, M(SD) | 7.05(13.885) | 4.14(9.176) | 2.00(0.044,5.016) | 0.046* | 0.979(0.947,1.011) | 0.187 |
| APACHEII, M(SD) | 15.09(6.292) | 17.86(6.025) | −4.124(−4.469,1.582) | 0.000*** | 1.052(0.999,1.108) | 0.054 |
| Caprini, M(SD) | 7.74(3.365) | 8.29(3.910) | −1.215(−1.456,0.346) | 0.226 | | |
| PH, M(SD) | 7.38(0.068) | 7.38(0.080) | −0.047(−.018,0.017) | 0.962 | | |
| PaO2, M(SD) | 130.36(54.111) | 125.43(54.473) | 0.745(−8.081,17.936) | 0.457 | | |
| PaCO2, M(SD) | 37.48(10.442) | 38.71(10.258) | −0.969(−3.717, 1.265) | 0.334 | | |
| K, M(SD) | 4.07(0.677) | 3.91(0.702) | 1.874(−.008,0.321) | 0.062 | | |
| Na, M(SD) | 135.84(4.702) | 136.64(6.957) | −1.191(−2.126, 0.523) | 0.235 | | |
| Ca, M(SD) | 1.12(0.100) | 1.11(0.159) | 0.437(−.027, 0.042) | 0.663 | | |
| CL, M(SD) | 106.68(11.236) | 107.48(5.639) | −0.668(−3.149, 1.553) | 0.505 | | |
| Blood glucose, M(SD) | 10.70(8.284) | 9.69(3.857) | 1.156(−.710, 2.732) | 0.249 | | |
| RBC [×10^12/L, M(SD)] | 3.60(1.681) | 4.21(5.289) | −1.124(−1.690, 0.467) | 0.263 | | |
| HBG [g/L, M(SD)] | 103.26(27.331) | 102.19(29.986) | 0.314(−5.688, 7.845) | 0.754 | | |
| HCT [%, M(SD)] | 31.73(10.634) | 30.89(9.396) | 0.670(−1.623, 3.297) | 0.504 | | |
| WBC [×10^9/L, M(SD)] | 12.33(11.005) | 12.20(6.015) | 0.108(−2.199, 2.453) | 0.914 | | |
| PLT [×10^9/L, M(SD)] | 184.34(109.861) | 174.07(98.543) | 0.792(−15.252, 35.787) | 0.429 | | |
| NEUT,[×10^9/L, M(SD)] | 13.50(46.894) | 11.34(7.462) | 0.455(−7.179, 11.494) | 0.650 | | |
| Lym [×10^9/L, M(SD)] | 5.82(69.858) | 0.82(0.468) | 0.710(−8.836, 18.819) | 0.478 | | |

(*Continued*)

**Table 2** (Continued).

| | ND Group (N=210) | SSD Group (N=99) | Univariate Model | | Multivariate Model | |
|---|---|---|---|---|---|---|
| | | | OR(95% CI) | P | OR(95% CI) | P |
| CRP(mg/L) | | | | 0.836 | | |
| <5.0 | 64(30.5) | 28(28.3) | | | | |
| 5.0–200 | 122(58.1) | 61(61.6) | | | | |
| >200 | 24(11.4) | 10(10.1) | | | | |
| hs-CRP>5.0, yes(%) | 147(70.0) | 70(70.7) | 0.967(0.572,1.632) | 0.899 | | |
| Mg [mmol/L, M(SD)] | 2.50(11.664) | 0.89(0.174) | 1.992(0.016, 3.191) | 0.048* | 0.941(0.750,1.182) | 0.603 |
| TP [g/L, M(SD)] | 55.56(12.083) | 60.55(42.769) | −1.56(−11.260, 1.281) | 0.118 | | |
| ALB [g/L, M(SD)] | 32.60(6.544) | 33.30(13.243) | −0.622(−2.913, 1.514) | 0.534 | | |
| Cr [umol/L, M(SD)] | 102.98(111.468) | 136.80(167.50) | −1.82(−70.407, 2.776) | 0.070 | | |
| TBil [umol/L, M(SD)] | 21.23(24.454) | 34.52(65.042) | −1.968(−26.666, 0.0990) | 0.052 | | |
| LAC [mmol/L, M(SD)] | 3.49(3.473) | 3.22(1.838) | 0.710(−.467, 0.995) | 0.478 | | |
| PCT [ng/mL, M(SD)] | 6.76(28.658) | 5.80(25.963) | 0.284(−5.712, 7.639) | 0.777 | | |
| FIB [g/L, M(SD)] | 3.42(2.465) | 3.41(1.434) | 0.041(−.514,0.536) | 0.967 | | |

**Notes**: [a]Taking the forced lying position as a reference, the risk of active lying position and passive lying position. *$p$<0.05, **$p$<0.01, ***$p$<0.001.
**Abbreviations**: ADL, activities of daily living; APACHE, Acute Physiology and Chronic Health Evaluation; BMI, Body Mass Index; CCI, Charlson Comorbidity Index; CI: confidence interval; Cr, creatinine; CRP, C-reactive protein; FIB, Fibrinogen; HCT, Red blood cell specific volume; HGB, hemoglobin; HR, Heart rate; hs-CRP, hypersensitive C-reactive protein; ICU, Intensive Care Unit; LAC, lactic acid; Lym, leukomonocyte; M, Mean; MFS, Morse Fall Scale; MMSE, Mini-mental State Examination; n, number; NEUT, neutrophil; NRS, Nutrition risk screening; OR, odds ratio; PCT, procalcitonin; PLT, Platelets; RBC, red blood cell count; RCSQ, Richards-Campbell Sleep Questionnaire; SD, Standard Deviation; SSD, Subsyndromal delirium; T, Temperature; TBIL, total bilirubin; TP, Total protein; WBC, leukocyte.

of mental illness (OR, 3.741; 95% CI, 1.136–12.324; P <0.05), auxiliary ventilation (OR, 3.364; 95% CI, 1.448–7.813; P <0.01), hemodialysis (OR, 11.369; 95% CI, 1.245–103.840; P <0.05), MMSE score (OR, 0.845; 95% CI, 0.789–0.904; P <0.001) and temperature ≥ 37.5 °C (OR, 3.686; 95% CI, 1.404–9.732; P <0.01) were independent risk factors for occurrence of SSD in ICU.

## Discussion

The prevalence and risk factors for SSD were evaluated in 309 ICU patients. The prevalence of probable SSD was 32.0%. A history of previous psychiatric illness was a statistically significant non-modifiable risk factor for high risk of SSD. The results showed that assisted ventilation, MMSE score, temperature ≥37.5°C, and haemodialysis were independent modifiable risk factors for SSD.

### Prevalence of Subsyndromal Delirium

The 32.0% prevalence of SSD was consistent with findings from other studies conducted in intensive care units. A previous study reported a prevalence of 33.9% in elderly Japanese patients with an average age of 72 years[14] and another study reported a prevalence of 33.3% in Canadian patients with an average age of 63 years.[25] Similar results were reported in post-operative cardiac patients.[16,26] SSD prevalence rates among elderly patients in hospitals, nursing homes and long-term care facilities range between 12.6% and 60.9%.[27] SSD prevalence varies across studies, which may be attributed to differences in the assessment tool and the selection of diagnostic criteria.[28] Cole et al[29] used the Confusion Assessment Method (CAM) to assess patients with two or more core symptoms of delirium as the diagnostic criteria for SSD. The results showed a lower incidence of SSD compared with using one or more core symptoms of delirium as the diagnostic criteria. In the present study, similar results were obtained using the ICDSC assessment method, whereby higher scores were associated with lower prevalence.

These findings indicate that physicians should explore the probability of SSD in older patients who are frail or have cognitive impairment.[30] Delirium symptoms are usually acute and change with time, resulting in a high rate of missed diagnoses. SSD is mainly associated with mild delirium symptoms and may have a higher rate of missed diagnoses than delirium. Therefore, the diagnostic threshold for assessment tools should be selected carefully to ensure increased sensitivity. Regular screening of frail ICU patients using a validated SSD screening tool can help in effective SSD diagnosis. However, SSD assessment currently requires use of diagnostic criteria or assessment tools for delirium and requires a long time to administer. Therefore, harmonization of SSD diagnostic criteria and construction of appropriate and convenient diagnostic tools can improve SSD detection rates.

## Risk Factors

Binary logistic regression analysis showed that previous history of mental illness, MMSE score, haemodialysis, mechanical ventilation and a body temperature ≥37.5 °C were associated with an increased risk of SSD in the ICU. Previous studies reported that history of psychiatric illness,[7] MMSE score[31,32] and temperature ≥37.5°C[7] were risk factors for SSD. Reduced cognitive reserve is an independent risk factor for the development of delirium and may be implicated in inflammatory response.[33] The results showed that patients that underwent haemodialysis had higher risk of SSD. However, the mechanisms underlying the development of psychiatric symptoms during dialysis have not been elucidated and the clinical presentation varies and is non-specific among patients. The potential clinical manifestations include dialysis-inadequate uremic encephalopathy, dialysis-related encephalopathy and cerebrovascular lesions.[34]

Mechanical ventilation is a major risk factor for delirium.[35] Mechanical ventilation increases intra-thoracic pressure and results in a decrease in blood return and unstable blood pressure. Mechanical ventilation in patients with hypertension aggravates the instability of blood pressure, affecting blood supply to the brain and the patient presents with hypoxia, which in turn induces delirium. In addition, prolonged mechanical ventilation can result in negative emotions, such as discomfort, fear and anxiety, thus increasing the stress response and affecting the patient's sleep and mental status, ultimately increasing the risk of delirium.

## Strengths and Limitations of the Study

The present study provides key information on factors associated with increased risk of SSD in ICU patients admitted at the Second Affiliated Hospital in Chongqing, southwest China. In the current study, assessment of patient was conducted by uniformly trained nurses, and experienced clinicians and psychiatrists, which improved the accuracy of estimating the prevalence of SSD and the relationship between risk factors and SSD prevalence. This study had some limitations. Firstly, although assessment using the ICDSC has some advantages over other delirium assessment scales, such as continuous recording of the status and degree of SSD, the ICDSC has a suboptimal specificity (64%) for use as a score assessment and monitoring of patients with several symptoms according to their scores.[20] It is suggested that a joint assessment of SSD by CAM-ICU and ICDSC can be used to solve the problem of continuous assessment of CAM-ICU dichotomous diagnosis and to improve the diagnostic specificity.[11] Secondly, although patients in a coma, ICU patients under mechanical ventilation and sedation were excluded from the study. Moreover, there was subjective assessment by nurses who could not distinguish between the sedated state and SSD. Thirdly, the patient's pre-admission cognitive level was not assessed in this study due to the emergency admission of the patients and chart review was used, which may be biased.

# Conclusion

The findings showed that almost a third of the patients admitted in the ICU had SSD. A history of previous psychiatric illness, MMSE scores, haemodialysis, a temperature ≥37.5°C and treatment with mechanical ventilation were associated with high risk of SSD occurrence. The present results provide a basis for clinical staff to effectively identify and monitor SSD patients and to formulate and provide targeted therapeutic care measures to patients. Nursing staff should pay attention to the management of such patients with high risk of SSD occurrence to prevent progression of SSD to delirium, thereby improving patient prognosis.

## Ethical Considerations

Ethical approval was obtained from the Ethics Committee of the Second Hospital of Chongqing Medical University (Date: 26 August 2021, Number: 2021-74).

## Funding

Chongqing Natural Science Foundation Project (CSTB2022NSCQ-MSX0816).

## Disclosure

The authors report no conflicts of interest in this work.

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