Intraoperative body temperature and emergence delirium in elderly patients after non-cardiac surgery: A secondary analysis of a prospective observational study

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Abstract

Background: Emergence delirium (ED) is a kind of delirium that occured in the immediate post-anesthesia period. Lower body temperature on post-anesthesia care unit (PACU) admission was an independent risk factor of ED. The present study was designed to investigate the association between intraoperative body temperature and ED in elderly patients undergoing non-cardiac surgery.

Methods: This study was a secondary analysis of a prospective observational study. Taking baseline body temperature as a reference, intraoperative absolute and relative temperature changes were calculated. The relative change was defined as the amplitude between intraoperative lowest/highest temperature and baseline reference. ED was assessed with the confusion assessment method for intensive care unit at 10 and 30 min after PACU admission and before PACU discharge.

Results: A total of 874 patients were analyzed with a mean age of 71.8 ± 5.3 years. The incidence of ED was 38.4% (336/874). When taking 36.0°C, 35.5°C, and 35.0°C as thresholds, the incidences of absolute hypothermia were 76.7% (670/874), 38.4% (336/874), and 17.5% (153/874), respectively. In multivariable logistic regression analysis, absolute hypothermia (lowest value <35.5°C) and its cumulative duration were respectively associated with an increased risk of ED after adjusting for confounders including age, education, preoperative mild cognitive impairment, American Society of Anesthesiologists grade, duration of surgery, site of surgery, and pain intensity. Relative hypothermia (decrement >1.0°C from baseline) and its cumulative duration were also associated with an increased risk of ED, respectively. When taking the relative increment >0.5°C as a threshold, the incidence of relative hyperthermia was 21.7% (190/874) and it was associated with a decreased risk of ED after adjusting above confounders.

Conclusions: In the present study, we found that intraoperative hypothermia, defined as either absolute or relative hypothermia, was associated with an increased risk of ED in elderly patients after non-cardiac surgery. Relative hyperthermia, but not absolute hyperthermia, was associated with a decreased risk of ED.

Registration: Chinese Clinical Trial Registry (No. ChiCTR-OOC-17012734).

Keywords: Hypothermia; Hyperthermia; Emergence delirium; Pain measurement; Cognitive dysfunction; Non-cardiac surgery; Aged; Post-anesthesia care unit

Introduction

Delirium is an acute brain dysfunction that is manifested by inattention, altered awareness, cognitive impairment, and sleep disturbance.[1] Early-onset of delirium in the immediate post-anesthesia period is considered emergence delirium (ED).[2] The incidence of ED varies from 4% to 20% in surgical adult patients.[3,4] In our previous report, its incidence reached 37% in the elderly.[5] ED is highly correlated with poor clinical outcomes, such as prolonged length of in-hospital stay, increased risk of pulmonary complication, postoperative delirium (POD, delirium within postoperative first 5 days), and readmission.[3,5,6]

The underlying mechanism of ED is multifactorial including predisposing factors (patient's baseline status, i.e., aging and poor cognitive function) and precipitating factors (perioperative new-onset triggers, i.e., emergency surgery, longer duration of surgery, deep anesthesia, and low body temperature).[5-8] Body temperature is considered one of the vital signs. In patients undergoing general anesthesia, physiological thermoregulation is disrupted which is manifested by the impaired threshold of sweating and shivering, reduction of vasoconstriction, and heat redistribution.[9] The incidence of hypothermia (i.e., core temperature <36.0°C) was as high as 44% in a population-based cohort study.[10]

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Previous studies showed that intraoperative hypothermia was associated with POD, but there was little data to elucidate its association with ED. The lowest intraoperative body temperature of patients with POD is about 34.5°C, which is 0.6°C lower than the value of non-delirious patients after cardiac surgery.[11] One observational study with a small sample size of 266 patients reported that lower body temperature on post-anesthesia care unit (PACU) admission was an independent risk factor of ED.[12] This result was in line with our previous analysis.[5] As we know, the body temperature on PACU admission was a result of intraoperative temperature management. Thus, it is deserved to investigate if intraoperative body temperature (i.e., hypothermia, hyperthermia, and their cumulative durations) was associated with ED.

The present study was designed to investigate the association between intraoperative temperature and ED in elderly patients undergoing non-cardiac surgery.

Methods

Ethics approval

This study was a secondary analysis of a prospective observational study. This study was approved by the Clinical Research Ethics Committee of Peking University First Hospital on August 4, 2017 (No. 2017[1419], Beijing, China) and was registered with the Chinese Clinical Trial Registry on September 19, 2017 (chictr.org.cn, ChiCTR-OOC-17012734), conducting from September 2017 to April 2019.[5] Written informed consent was obtained from all participants or their legal representatives. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation and with the *Declaration of Helsinki*, as revised in 2000.

Participants

The present study included elderly patients (aged 65–90 years) who underwent non-cardiac major surgery (expected duration ≥ 2 h) under general anesthesia and were admitted to PACU after the surgery accomplished. Exclusion criteria were as follows: (1) disagreed to participate; (2) diagnosed neuropsychological disorders, that is, schizophrenia, epilepsy, Parkinson's disease, and myasthenia gravis; (3) comatose, dementia, or language barrier which impeded communication and assessment; (4) history of neurosurgical procedures; (5) American Society of Anesthesiologists (ASA) grade of IV or higher; and (6) no record of intraoperative core temperature.[5]

Anesthesia and perioperative care

No patient received premedication (such as benzodiazepines or opioids). After standard monitoring including blood pressure, heart rate, pulse oxygenation, electrocardiography, and end-tidal carbon dioxide, general anesthesia was inducted and maintained by propofol and/or sevoflurane with opioids (sufentanil and/or remifentanil) for analgesia. Advanced monitoring including invasive arterial pressure and central venous pressure could be used in necessary. Medical heat conserving devices (i.e., forced-air warmings, fluid heaters, and under-body warming blankets) were used to manage perioperative body temperature according to routine practice.

At the end of surgery, a combination of neostigmine (0.05 mg/kg) and atropine (0.02 mg/kg) was administered to reverse residual neuromuscular blockage. The decision of extubation was followed based on the following criteria: (1) awaken easily; (2) reflexes sufficient to protect the airway; (3) the respiratory rate should be 10 to 30 breaths/min, and the breathing volume should be >6 mL/kg; and (4) systolic blood pressure ≥90 mmHg and heart rate ≤100 beats/min.

Patients were monitored in the PACU for at least 30 min. A numeric rating scale (NRS, an 11-point scale where 0 = no pain and 10 = the worst pain) was used to assess pain severity, and opioid or non-steroid anti-inflammatory drugs would be administered to relieve pain intensity (NRS ≥4). Patients with hypothermia (<36.0°C) were treated with warm air blankets.

Perioperative body temperature monitoring

According to routine clinical practice in our center, inpatients received measurements of axillary temperature by mercury thermometer at 08:00 to 09:00 every morning in the general ward. We employed the temperature one day before surgery as a baseline reference, because patients were transferred to the operating room at 07:00 to 08:00 and they would miss the monitoring time point on surgery day.

Intraoperative core temperature was monitored at the upper-medium part of esophagus by the single-use thermistor. After anesthesia induction, a thermistor was inserted through nasal cavity with a depth of 15 to 20 cm (referred to as the distance from ala nasi to earlobe on the same side). The intraoperative temperature was recorded every 10 S by the electronic anesthesia information management system automatically.

Variability of intraoperative temperature was calculated in two approaches: absolute and relative temperature changes. For an absolute change, hypothermia was diagnosed if the lowest temperature value during surgery was lower than a predefined threshold (i.e., 36.0°C, 35.5°C, and 35.0°C, respectively), and the highest temperature values >37.0°C and >37.5°C were considered as hyperthermia, respectively. For a relative change, hypothermia was diagnosed if the relative decrement from baseline to lowest core temperature was more than a predefined amplitude (i.e., 0.5°C, 1.0°C, and 1.5°C). Relative hyperthermia was diagnosed if the relative increment from baseline temperature to highest temperature was >0.5°C and 1.0°C, respectively.

Outcomes

The primary outcome was the incidence of ED during PACU stay. ED was assessed with the confusion assessment method for intensive care unit (CAM-ICU) at 10 min after PACU admission, 30 min after PACU

admission and before PACU discharge.[5,13] A patient was diagnosed with ED if he/she suffered at least one episode of delirium at the above time points. According to the Richmond Agitation–Sedation Scale (RASS) at assessment, we classified ED into three subtypes, that is, hyperactive (with a consistently positive RASS, from +1 to +4), hypoactive (with a consistently neutral or negative RASS, from 0 to −3), and mixed.[13,14]

To ensure the concordance and accuracy of delirium assessments, all investigators were trained to use the CAM-ICU and the confusion assessment method (CAM) for POD assessment by an experienced psychiatrist.[15,16] Lectures and simulator training were included.[5] Investigators who performed delirium assessments did not participate in the perioperative care of the enrolled patients.[5]

Data collection and postoperative follow-up

Basic demographics (age, education, comorbid conditions, smoking, drinking, Charlson Comorbidity Index, and ASA grade) were collected.[17] The Mini-Mental State Examination (MMSE, scores ranged from 0 to 30, with a better function indicated by a higher score) was used to measure baseline cognitive ability one day before surgery. Mild cognitive impairment (MCI) was defined as MMSE <27. Anesthetic types, surgery site, and the length of the surgery were recorded as intraoperative data. During the hospital stay, patients were monitored twice a day for delirium and complications other than delirium until the 5th day after surgery.

We provided weekly follow-ups for patients from the 6th day after surgery till they were discharged. A telephone interview was conducted on the 30th day after surgery if patients were discharged from the hospital.[5]

Statistical analysis

Continuous variables with normal distribution were presented as mean ± standard deviation and analyzed by independent sample *t* test or analysis of variance. Continuous variables with non-normal distribution were presented as median (interquartile) and analyzed by Mann–Whitney *U* test or Kruskal–Wallis test. Categorical variables were presented as *n* (%) and analyzed by chi-squared test or Fisher exact test.

Patients were divided into two groups, that is, those with ED and those without ED. For the primary outcome, the incidence of ED was presented as *n* (%). A multivariable logistic regression model (Backward: Wald) was employed to investigate the association between intraoperative body temperature and ED and adjusted for age, education, preoperative MCI, ASA grade, duration of surgery, site of surgery, and pain intensity. The selection of confounders was based on baseline and perioperative variables with statistical significance (i.e., $P < 0.05$) in univariable logistic regression analysis which was used to screen the potential associations between these variables and ED. The association between cumulative duration of hypothermia or hyperthermia and ED was depicted by restricted cubic spline (RCS) analysis with four knots located at the 5th, 25th, 75th, and 95th percentiles.[18] Their associations with ED were also analyzed by a multivariable logistic regression model (Backward: Wald).

Subgroup analysis was conducted to investigate if the above temperature parameters were associated with ED by multivariable logistic analysis (Backward: Wald) in patients with different ages (>75-year-old or 65–75 years old) and sex (female or male). For sensitivity analysis, multivariable logistic analysis (Backward: Wald) was also employed to investigate if the above temperature parameters were associated with different types of ED (hypoactive, hyperactive, and mixed ED).

The incidences of POD within postoperative 5 days and non-delirium complications within 30 days were presented as *n* (%), and differences between groups were analyzed by chi-squared test. The length of PACU and hospital stay after surgery was presented as median (interquartile) and compared by Mann–Whitney *U* test.

Data analyses were performed with the SPSS 25.0 software (IBM SPSS Inc., Chicago, IL, USA) and R (version 3.6.3; R Development Core Team, Vienna, Austria). A two-sided $P < 0.05$ was considered statistically significant. No imputation of missing variables was performed.

Results

Participants and baseline temperature

Nine hundred and fifteen patients were enrolled during the study period. Among these patients, 41 patients were excluded from this study because of lack of intraoperative temperature data. Eight hundred and seventy-four patients were included in the final analysis with a mean age of 71.8 ± 5.3 years [Supplementary Figure 1, http://links.lww.com/CM9/B246]. About 1.3% (11/874) of patients died within postoperative 30 days.

Baseline temperature in ED patients was similar with that of patients without ED [36.4 ± 0.4°C *vs.* 36.4 ± 0.3°C, $P = 0.222$; Table 1 and Supplementary Table 1, http://links.lww.com/CM9/B246].

Incidence of ED

About 38.4% (336/874) of patients developed ED. The incidences were 18.8% (63/336) for hyperactive ED, 77.0% (259/336) for hypoactive delirium, and 4.2% (14/336) for mixed delirium, respectively. The incidence of delirious event was 38.3% (335/874) at 10 min after PACU admission, and reduced to 18.2% (159/874) at 30 min after PACU admission and 7.10% (62/874) at PACU discharge.

Association between absolute change of temperature and ED

When taking temperatures 36.0°C, 35.5°C, and 35.0°C as thresholds, the overall incidences of intraoperative hypothermia were 76.7% (670/874), 38.4% (336/874), and 17.5% (153/874), respectively [Table 2]. In multivariable

Table 1: Characteristics of elderly patients with or without emergence delirium after non-cardiac surgery.

Variables	Total ($n = 874$)	Patients without ED ($n = 538$)	Patients with ED ($n = 336$)	Statistics	*P* values
Age (years)	71.8 ± 5.3	70.9 ± 4.8	73.1 ± 5.8	5.927	<0.001
Male	518 (59.3)	332 (61.7)	186 (55.4)	3.458	0.063
BMI (kg/m^2)	24.1 ± 3.5	24.2 ± 3.3	24.1 ± 3.8	0.399	0.690
Education (year)	9 (6, 13)	10 (7, 15)	9 (6, 12)	–3.526	<0.001
Preoperative comorbidity					
Stroke[*]	50 (5.7)	33 (6.1)	17 (5.1)	0.443	0.506
Pulmonary disease[†]	63 (7.2)	35 (6.5)	28 (8.3)	1.033	0.309
Coronary heart disease	127 (14.5)	68 (12.6)	59 (17.6)	4.031	0.045
Hepatic dysfunction[‡]	43 (4.9)	24 (4.5)	19 (5.7)	0.630	0.427
Chronic smoking[§]	206 (23.6)	140 (26.0)	66 (19.6)	4.673	0.031
Alcoholism[‖]	136 (15.6)	92 (17.1)	44 (13.1)	2.525	0.112
Malignant tumor	96 (11.0)	59 (11.0)	37 (11.0)	0.000	0.983
History of surgery	454 (51.9)	261 (48.5)	193 (57.4)	6.604	0.010
ASA grade				5.905	0.015
II	641 (73.3)	410 (76.2)	231 (68.8)		
III	231 (26.4)	127 (23.6)	104 (31.0)		
IV	2 (0.2)	1 (0.2)	1 (0.3)		
MMSE score	27 (25, 28)	27 (26, 28)	26 (24, 28)	6.938	<0.001
MCI[¶]	384 (48.9)	189 (35.1)	195 (58.0)	44.054	<0.001
CCI score	2 (2, 3)	2 (2, 3)	2 (2, 3)	0.072	0.772
Baseline temperature (°C)					
As continuous variable	36.4 ± 0.3	36.4 ± 0.3	36.4 ± 0.4	1.223	0.222
As categorical variable				4.654	0.460
>37.5	3 (0.3)	2 (0.4)	1 (0.3)		
37.0–37.5	18 (2.1)	11 (2.0)	7 (2.1)		
36.5–37.0	224 (25.6)	125 (23.2)	99 (29.5)		
36.0–36.5	478 (54.7)	307 (57.1)	171 (50.9)		
35.5–36.0	137 (15.7)	84 (15.6)	53 (15.8)		
≤35.5	14 (1.6)	9 (1.7)	5 (1.5)		

Categorical variables were presented as *n* (%), and continuous variables were presented as mean ± SD or median (Q_1, Q_3), depending on the distribution. Statictics were presented as *t* value; χ^2 value; Fisher's exact test or *Z* value. [*] Includes hemorrhagic and ischemic stroke. [†] Pulmonary disease included chronic obstructive pulmonary disease and asthma. [‡] Hepatic dysfunction was defined as alanine transaminase and/or aspartate transaminase >5 times the upper normal limit. [§] Chronic smoking was defined as half a pack of cigarettes per day for at least two years. [‖] Two drinks or more daily, or weekly consumption of the equivalent of 150 g of alcoholism. [¶] MCI was defined as MMSE score <27. ASA: American Society of Anesthesiologists; BMI: Body mass index; CCI: Charlson Comorbidity Index; ED: Emergence delirium; MCI: Mild cognitive impairment; MMSE: Mini-Mental State Examination; SD: Standard deviation.

logistic regression analysis, temperature <35.5°C was associated with an increased risk of ED (odds ratio [OR] 1.551, 95% confidence interval [CI] 1.151–2.090, $P = 0.004$) after adjusting for confounders including age, education, preoperative MCI, ASA grade, duration of surgery, site of surgery, and pain intensity [Table 3 and Supplementary Table 2, http://links.lww.com/CM9/B246]. For sensitivity analysis, we found that temperature <35.5°C was associated with hypoactive ED, but not the other subtypes [Supplementary Table 3, http://links.lww.com/CM9/B246].

When taking temperatures >37.0°C and >37.5°C as thresholds, the incidences of hyperthermia were 11.4% (100/874) and 2.1% (18/874), respectively, but both temperatures >37.0°C (OR 0.708, 95% CI 0.442–1.136, $P = 0.152$) and >37.5°C (OR 0.746, 95% CI 0.260–2.133, $P = 0.585$) were not associated with ED.

Association between relative change of temperature and ED

When taking the relative decrement from baseline temperature to lowest temperature >0.5°C, 1.0°C, and 1.5°C as thresholds, the incidences of hypothermia were 65.0% (568/874), 34.8% (304/874), and 18.1% (158/874), respectively. In multivariable logistic regression analysis, decrement >1.0°C was associated with an increased risk of ED (OR 1.869, 95% CI 1.375–2.542, $P < 0.001$) after adjusting for confounders including age, education, preoperative MCI, ASA grade, duration of surgery, site of surgery, and pain intensity [Supplementary Tables 2, http://links.lww.com/CM9/B246 and 4, http://links.lww.com/CM9/B246]. For sensitivity analysis, we found that decrement >1.0°C was associated with hypoactive ED, but not the other subtypes [Supplementary Table 3, http://links.lww.com/CM9/B246].

When taking the increment from baseline temperature to highest temperature >0.5°C as threshold, the incidence of relative hyperthermia was 21.7% (190/874) and it was associated with a decreased risk of ED (OR 0.617, 95% CI 0.428–0.888, $P = 0.009$) after adjusting above confounders. For sensitivity analysis, we found that relative increment >0.5°C was associated with hypoactive ED, but not the other subtypes [Supplementary Table 3,

Table 2: Perioperative data of elderly patients with or without emergence delirium after non-cardiac surgery.

Variables	Total ($n = 874$)	Patients without ED ($n = 538$)	Patients with ED ($n = 336$)	Statistics values	*P* values
Intraoperative data					
Type of anesthesia				3.310	0.191
General anesthesia	420 (48.1)	247 (45.9)	173 (51.5)		
General anesthesia combined nerve block	429 (49.1)	277 (51.5)	152 (45.2)		
General anesthesia combined epidural anesthesia	25 (2.9)	14 (2.6)	11 (3.3)		
Site of surgery				10.018	0.018
Thoracic	183 (20.9)	126 (23.4)	57 (17.0)		
Abdominal	516 (59.0)	319 (59.3)	197 (38.2)		
Orthopedic	159 (18.2)	83 (15.4)	76 (22.6)		
Superficial	16 (1.8)	10 (1.9)	6 (1.8)		
Duration of surgery (hours)	3.1 (2.5, 4.0)	3.0 (2.4, 3.9)	3.3 (2.6, 4.1)	3.023	0.003
Intraoperative medication					
Use of sevoflurane	287 (32.8)	168 (31.2)	119 (35.4)	1.646	0.199
Use of etomidate	671 (76.8)	403 (74.9)	268 (79.8)	2.734	0.098
Use of midazolam	189 (21.6)	118 (21.9)	71 (21.1)	0.079	0.779
Use of dexmedetomidine	417 (47.7)	250 (46.5)	167 (49.7)	0.867	0.352
Dosage of dexmedetomidine (μg)	0 (0, 40)	0 (0, 40)	0 (0, 40)	−0.873	0.383
Dosage of sufentanil (μg)	40 (25, 70)	40 (25, 68)	41 (25, 75)	−1.283	0.199
Dosage of rocuronium (mg)	50 (40, 50)	50 (40, 50)	50 (40, 50)	−0.360	0.719
Dosage of cisatracurium (mg)	10 (6, 18)	10 (6, 18)	12 (6, 18)	−0.223	0.223
Intraoperative infusion volume (mL)	2250 (1600, 2931)	2100 (1600, 2600)	2375 (1813, 3200)	−4.800	<0.001
Allogeneic blood transfusion	79 (9.0)	33 (6.1)	46 (13.7)	14.365	<0.001
Hypotension[*]	143 (16.4)	92 (17.1)	51 (15.2)	0.558	0.455
Alderete score at PACU admission[†]				1.403	0.236
10	675 (88.4)	423 (90.4)	252 (86.4)		
9	89 (11.6)	50 (10.6)	39 (13.4)		
Absolute change of intraoperative temperature					
Lowest absolute temperature	35.5 ± 0.7	35.5 ± 0.7	35.4 ± 0.7	2.417	0.016
<36.0°C	670 (76.7)	401 (74.5)	269 (80.1)	3.528	0.060
Cumulative duration (min)	99 (2, 167)	82 (0, 154)	125 (27, 186)	−1.547	<0.001
<35.5°C	336 (38.4)	186 (34.6)	150 (44.6)	8.863	0.003
Cumulative duration (min)	0 (0, 49)	0 (0, 24)	0 (0, 74)	−3.490	<0.001
<35.0°C	153 (17.5)	86 (16.0)	67 (19.9)	2.241	0.134
Cumulative duration (min)	0 (0, 0)	0 (0, 0)	0 (0, 0)	−4.577	0.122
Highest absolute temperature	36.5 ± 0.5	36.6 ± 0.5	36.5 ± 0.4	1.945	0.052
>37.0°C	100 (11.4)	67 (12.5)	33 (9.8)	1.414	0.234
Cumulative duration (min)	0 (0, 0)	0 (0, 0)	0 (0, 0)	−1.210	0.226
>37.5°C	18 (2.1)	12 (2.2)	6 (1.8)	0.203	0.652
Cumulative duration (min)	0 (0, 0)	0 (0, 0)	0 (0, 0)	−0.426	0.670
Relative change of intraoperative temperature					
Relative hypothermia[‡]					
Relative decrement >0.5°C	568 (65.0)	346 (64.3)	222 (66.1)	0.281	0.596
Cumulative duration (min)	52 (0, 154)	36 (0, 133)	97 (0, 183)	−3.543	<0.001
Relative decrement >1.0°C	304 (34.8)	160 (29.7)	144 (42.9)	15.688	<0.001
Cumulative duration (min)	0 (0, 50)	0 (0, 6)	0 (0, 91)	−4.330	<0.001
Relative decrement >1.5°C	158 (18.1)	88 (16.4)	70 (20.8)	2.799	0.094
Cumulative duration (min)	0 (0, 0)	0 (0, 0)	0 (0, 0)	−1.799	0.072
Relative hyperthermia[§]					
Relative increment >0.5°C	190 (21.7)	129 (24.0)	61 (18.2)	4.122	0.042
Cumulative duration (min)	0 (0,0)	0 (0, 0)	0 (0, 0)	−2.069	0.039
Relative increment >1.0°C	33 (3.8)	24 (4.5)	9 (2.7)	1.809	0.179
Cumulative duration (min)	0 (0, 0)	0 (0, 0)	0 (0, 0)	−1.386	0.166
PACU data					
Length of stay in PACU (min)	40 (35, 50)	40 (30, 50)	45 (35, 55)	−5.134	<0.001
≤30	208 (23.8)	147 (27.3)	61 (18.2)	11.339	0.003
30–60	596 (68.2)	355 (66.0)	241 (71.7)		
>60	70 (8.0)	36 (6.7)	34 (10.1)		

(*continued*)

Table 2
(continued).

Variables	Total ($n = 874$)	Patients without ED ($n = 538$)	Patients with ED ($n = 336$)	Statistics values	*P* values
Pain intensity				15.436	<0.001
High (NRS ≥7)	2 (0.2)	0 (0)	2 (0.6)		
Medium (4 ≤ NRS < 7)	215 (24.6)	111 (20.6)	104 (31.0)		
Low (NRS <4)	657 (75.2)	427 (79.4)	230 (68.5)		
Use of sufentanil	47 (5.4)	24 (4.5)	23 (6.8)	2.311	0.128
Tympanic temperature					
At arrival of PACU	36.1 (0.5)	36.2 (0.5)	36.1 (0.5)	3.693	<0.001
At discharge of PACU	36.3 (0.4)	36.3 (0.4)	36.3 (0.4)	1.846	0.065
Rewarm	382 (43.7)	211 (39.2)	171 (50.9)	11.455	0.001
Postoperative data					
Delirium within 5 days	102 (11.7)	44 (8.2)	58 (17.3)	16.555	<0.001
Non-delirium complications[¶]	86 (9.8)	44 (8.2)	42 (12.5)	4.354	0.037
Postoperative LOS (day)	8 (6, 11)	8 (6, 10)	8 (6, 12)	−2.667	0.008

Categorical variables were presented as *n* (%), and continuous variables were presented as mean ± SD or median (Q_1,Q_3), depending on the distribution. Statictics were presented as *t* value; χ^2 value; Fisher's exact test or *Z* value. [*] Hypotension was defined as mean arterial pressure <65 mmHg and lasted for >20 min. [†] Alderete score was used to evaluate if patient was sufficiently recovered from general anesthesia by level of consciousness, breath, stability of circulation, tension of muscle and peripheral pulse oxygen saturation. Each item is scored by 0 to 2 according to severity and Alderete score ≥9 is considered sufficient recovery. [‡] Relative hypothermia was defined as relative decrement from baseline temperature to lowest core temperature >0.5°C, 1.0°C, and 1.5°C, respectively. [§] Relative hyperthermia was defined as relative increment from baseline temperature to highest core temperature >0.5°C and 1.0°C, respectively. [||] POD was defined as delirium that occurred in the general wards during postoperative days 1 to 5 and was assessed with the CAM twice daily (8:00–10:00 am, 18:00–20:00 pm).[5] [¶] Any new onset medical conditions, but not delirium, that adversely affect patients' recovery and require medical intervention within 30 days, that is, grade II or higher on the Clavien–Dindo classification. CAM: Confusion assessment method; ED: Emergence delirium; LOS: Length of in-hospital stay; NRSs: Numeric rating scales; PACU: Post-anesthesia care unit; POD: Postoperative delirium; SD: Standard deviation.

Table 3: Association between absolute hypothermia and emergency delirium.

Variables	Univariable		Multivariable	
	OR (95% CI)	*P* values	OR (95% CI)	*P* values
Age (per year increase)	1.079 (1.051–1.108)	<0.001	1.071 (1.042–1.102)	<0.001
Education (per year increase)	0.948 (0.920–0.977)	0.001	–	–
Preoperative MCI (yes)[*]	2.554 (1.931–3.378)	<0.001	2.340 (1.726–3.172)	<0.001
ASA grade (per grade increase)	1.448 (1.073–1.955)	0.016	–	–
Duration of surgery (per hour increase)	1.124 (1.004–1.260)	0.043	1.160 (1.028–1.310)	0.016
Site of surgery	1.356 (1.104–1.665)	0.004	1.292 (1.033–1.616)	0.025
Pain intensity (per grade increase)	1.929 (1.359–2.738)	<0.001	1.683 (1.211–2.340)	0.002
Intraoperative hypothermia (yes)[†]	1.526 (1.155–2.017)	0.003	1.551 (1.151–2.090)	0.004

[*] MCI was defined as MMSE score <27. [†] Intraoperative hypothermia was defined as the lowest temperature value during surgery was <35.5°C. We also tested if absolute temperature value <36.0°C and <35.0°C were associated with ED by entering them into the above multivariable logistic regression analysis respectively. Both absolute temperature value <36.0°C (OR 0.863, 95% CI 0.724–1.029, $P = 0.101$) and <35.0°C (OR 1.285, 95% CI 0.880–1.875, $P = 0.194$) were not related with ED respectively after adjusting for above confounders. ASA: American Society of Anesthesiologists; CI: Confidence interval; ED: Emergence delirium; MCI: Mild cognitive impairment; MMSE: Mini-Mental State Examination; OR: Odds ratio.

http://links.lww.com/CM9/B246]. However, when taking the increment from baseline temperature to highest temperature >1.0°C as threshold, the incidence of relative hyperthermia was 3.8% (33/874) and it was not associated with ED (OR 0.586, 95% CI 0.259–1.326, $P = 0.200$).

Association between cumulative duration of hypothermia/hyperthermia and ED

The association between cumulative duration of hypothermia/hyperthermia and ED was depicted by RCS analysis [Figures 1 and 2].

For absolute temperature change, multivariable logistic regression analysis showed that cumulative duration of temperatures <36.0°C (OR 1.003, 95% CI 1.002–1.005, $P < 0.001$) and <35.5°C (OR 1.004, 95% CI 1.001–1.006, $P = 0.001$) were associated with an increased risk of ED [Supplementary Table 5, http://links.lww.com/CM9/B246]. Cumulative duration of absolute hyperthermia (either >37.0°C or >37.5°C) was not associated with ED [Supplementary Table 5, http://links.lww.com/CM9/B246].

For relative change, multivariable logistic regression analysis showed that cumulative duration of decrements

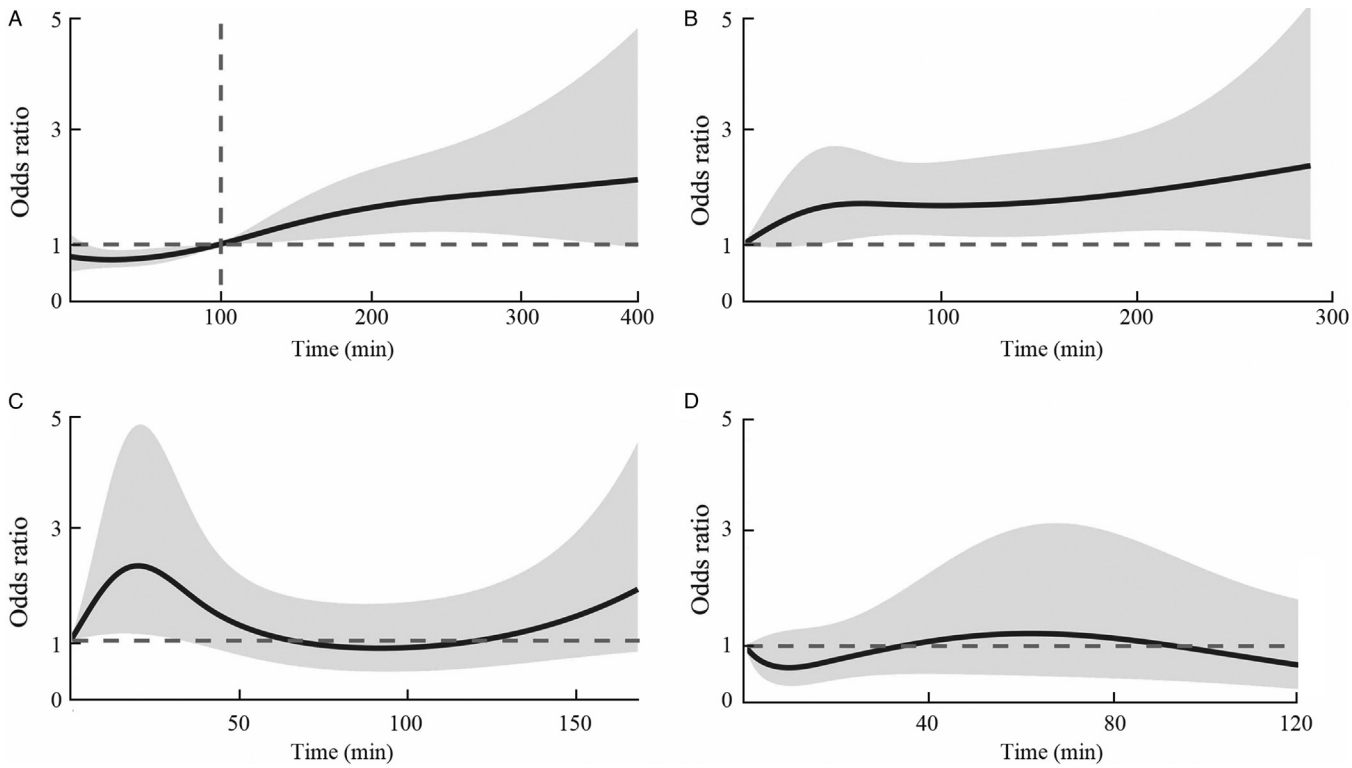

Figure 1: RCS of cumulative duration of absolute temperature change and ED. The association between cumulative duration of absolute temperature change and ED using RCS analysis with four knots located at the (A) 5th, (B) 25th, (C) 75th, and (D) 95th percentiles. RCS analysis showed that cumulative duration of temperatures <36.0°C (OR 1.003, 95% CI 1.002–1.005, $P < 0.001$) and <35.5°C (OR 1.004, 95% CI 1.001–1.006, $P = 0.001$) were associated with an increased risk of ED, respectively. The shaded areas are 95% CIs. *P* value of non-linear association of RCS A is 0.469. *P* value of non-linear association of RCS B is 0.277. *P* value of non-linear association of RCS C is 0.053. *P* value of non-linear association of RCS D is 0.325. CI: Confidence interval; ED: Emergence delirium; OR: Odds ratio; RCS: Restricted cubic spline analysis.

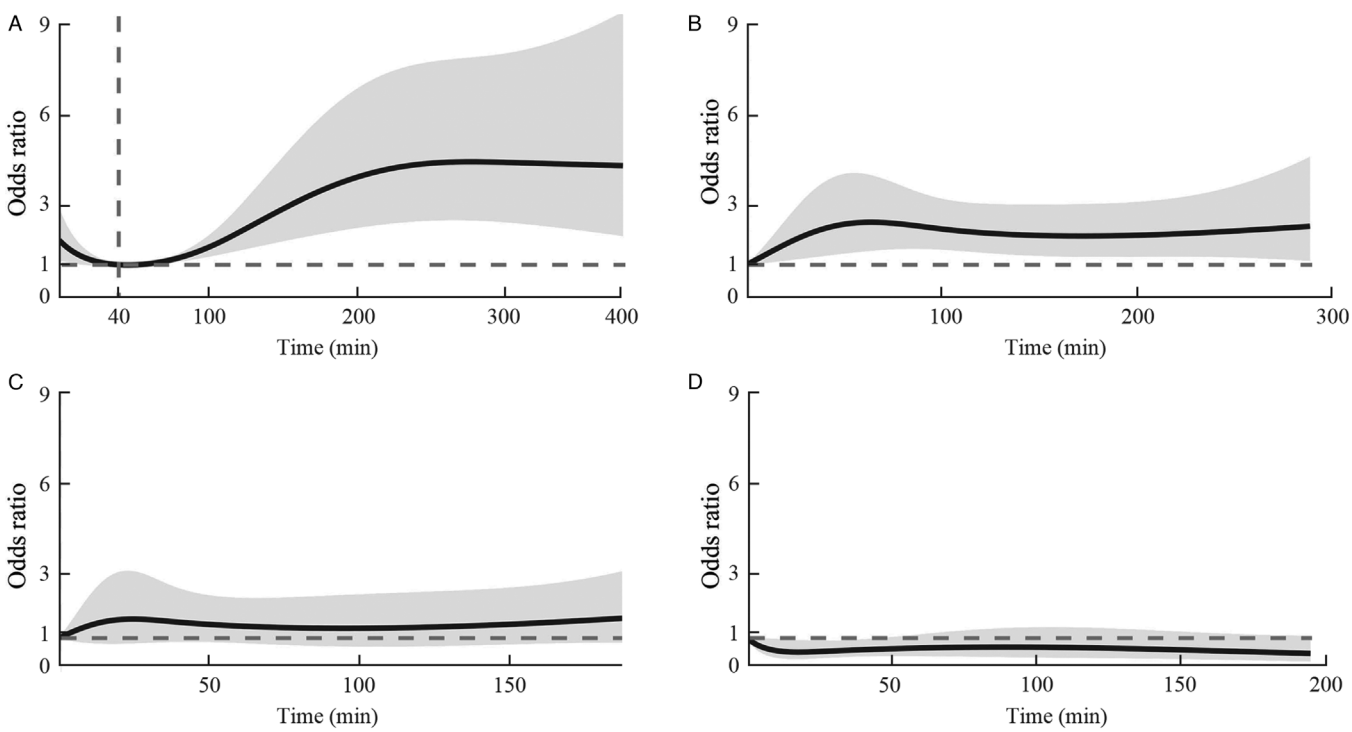

Figure 2: RCS of cumulative duration of relative temperature change and ED. The association between cumulative duration of relative temperature change and ED using RCS analysis with four knots located at the (A) 5th, (B) 25th, (C) 75th, and (D) 95th percentiles. RCS analysis showed that cumulative duration of relative decrements >0.5°C (OR 1.003, 95% CI 1.002–1.005, $P < 0.001$) and >1.0°C (OR 1.004, 95% CI 1.002–1.006, $P < 0.001$) were associated with an increased risk of ED, respectively. The shaded areas are 95% CIs. *P* value of non-linear association of RCS A is 0.034. *P* value of non-linear association of RCS B is 0.031. *P* value of non-linear association of RCS C is 0.540. *P* value of non-linear association of RCS D is 0.128. CI: Confidence interval; ED: Emergence delirium; OR: Odds ratio; RCS: Restricted cubic spline analysis.

>0.5°C (OR 1.003, 95% CI 1.002–1.005, $P < 0.001$) and >1.0°C (OR 1.004, 95% CI 1.002–1.006, $P < 0.001$) were associated with an increased risk of ED, respectively [Supplementary Table 5, http://links.lww.com/CM9/B246]. Both cumulative duration of increments >0.5°C and >1.0°C were not associated with ED [Supplementary Table 5, http://links.lww.com/CM9/B246].

Discussion

In the present study, we found that intraoperative hypothermia, defined as either absolute or relative hypothermia, was associated with an increased risk of ED in elderly patients undergoing non-cardiac surgery. Relative hyperthermia, but not absolute hyperthermia, was associated with decreased risk of ED.

ED was diagnosed by CAM-ICU which had been validated in Chinese patients. One strength of our study was that all researchers received delirium assessment training before and during the study. However, the definition and diagnostic criteria of ED deserve further discussion. First, there is a lack of optimal instruments to diagnose ED. CAM-ICU has been used in several studies to assess ED.[3,13,19,20] Taking the criteria of delirium in the Diagnostic and Statistical Manual of Mental Disorders 4th edition as a standard reference, the specificity of CAM-ICU to diagnose ED in PACU is about 98% (95% CI 88–100%).[21] This indicates that a positive CAM-ICU do represent true ED. To be noted, multiple assessments are proposed to overcome its lower sensitivity (28%, 95% CI 16–45%). Second, it's hard to distinguish hypoactive ED from delayed emergence. Altered consciousness level, a major characteristic of delirium, is used to distinguish ED from delayed emergence. For example, diagnosis of ED was established in patients with RASS score ≥+1, or patients with RASS score ≤−2.[12,22] Major deficit of this method is omission diagnosis of some hypoactive ED. In the present study, 108 patients presented RASS score ≤−2 and 360 patients presented RASS score ≤−1. Only 245 of them were diagnosed as hypoactive ED at first 10 min in PACU. Some scholars proposed another approach that ED occurs after a "lucid interval" from an anesthesia emergence whereas delayed emergence is an "extension" from general anesthesia.[21,23] But this perspective is still in controversy.[24] Aldrete score has been widely used to reflect if a patient has an appropriate recovery of wakefulness, hemodynamic, and respiratory stability from general anesthesia.[21,25] In the present study, patients were extubated in the operating room and presented Aldrete score ≥9 at PACU admission. This indicated that these patients experienced a "lucid interval" from anesthesia. At last, both ED and delayed emergence are associated with poor outcomes and deserve further investigation even if the overlapping clinical manifestations between them impede us to distinguish them.

A previous study had reported the association between body temperature on PACU admission and ED.[12] In our previous study, the result showed that the incidence of ED was 1.5 folds higher in patients with tympanic temperature <36°C on PACU admission.[5] As we know, the temperature on PACU admission was the result of intraoperative body temperature management. Up to now, there is a lack of data to elucidate the association between intraoperative body temperature and ED. Based on the comprehensive analysis of these data, the present study provides more information on the association between intraoperative body temperature and ED.[5]

There was little data about the association between intraoperative body temperature and ED, but previous studies showed that intraoperative hypothermia was associated with an increased risk of POD in patients undergoing surgery.[11,26] Several questions had to be addressed to interpret the result. The first question was what's the appropriate threshold of hypothermia? One major concern was that the chosen threshold would significantly influence the incidence of hypothermia. Several thresholds, such as 35.0°C, 35.5°C, and 36.0°C, have been used in literature.[27-29] Our result showed that the incidence of hypothermia varied from 17.5% to 76.7% by using different thresholds. Multivariable logistic regression analysis and RCS analysis showed that absolute hypothermia (<35.5°C) and its cumulative duration were associated with an increased risk of ED which suggested that 35.5°C could be selected as the potential threshold for hypothermia. The second question was which one, absolute threshold or relative threshold, was better? Absolute threshold has been used in most studies because it was easy to be grasped and managed by healthcare providers. But if taken 36.0°C as threshold, 151 patients with baseline temperature <36.0°C would be misdiagnosed as hypothermia in our present study. Unlike absolute change, relative change of temperature value reflected the amplitude of intraoperative temperature in an individual. Although the conception of "relative hypothermia" is still unclear, we did find that the decrement from baseline temperature >1.0°C was associated with an increased risk of ED. We also noticed that decrement >1.5°C was not associated with ED. This was not consistent with our logic that the severity of decrement was positively correlated with ED. The underlying reason might be its low incidence (only 88 patients in non-ED group and 70 patients in ED group), which yielded insufficient power to test the hypothesis. The third question was if cumulative duration of hypothermia was associated with ED. Most studies usually employed a single value to diagnose hypothermia which could not reflect the effect of time-weighted hypothermia on clinical outcomes. The present study found that the cumulative duration of hypothermia was associated with ED and their association was depicted by RCS analysis. This indicated that perioperative temperature management should be focused not only on the value of temperature but also cumulative duration of hypothermia.

An interesting phenomenon in the present study was that relative hyperthermia (increment from baseline temperature >0.5°C) was associated with decreased risk of ED. There was little data to elucidate the association between intraoperative relative hyperthermia and ED. A cohort study showed hyperthermia (i.e., >38.5°C) was associated with increased risk of POD in surgical patients.[30] However, the incidence of intraoperative hyperthermia is very low. Only 18 patients experienced the highest

absolute temperature >37.5°C in the present study. Taking relative increment from baseline temperature >0.5°C as threshold, the number of relative hyperthermia patients would reach up to 190. The baseline temperature of all patients was about 36.4°C whereas the highest intraoperative temperature was about 36.5°C. It seemed that relative increment >0.5°C was probably mild relative hyperthermia because the body temperatures of most patients would still be in the normal range after this increment. However, relative hyperthermia should be explored thoroughly in further studies about the classification of its severity and effect on other clinical outcomes.

In the present study, we noticed that delirious patients suffered lower body temperature on arrival at PACU and recovered to normal at discharge. This might be the reason why the incidence of ED significantly decreased across time during PACU. However, the available evidence was not sufficient to answer if therapies to maintain intraoperative normal body temperature could improve patients' prognosis in perioperative settings. Compared with the conventional therapy group (body temperature between 36.0°C and 37.0°C), mild hypothermia therapy (body temperature between 34.0°C and 35.0°C) was associated with lower levels of serum non-specific enzyme and S-100β in patients undergoing repair surgery of acute Stanford type A aortic dissection.[31] But the incidence of delirium or permanent neurological dysfunction showed no statistical difference between the two groups. Compared with the classical cooling protocol (32.0–34.0°C), modified mild hypothermia (34.0–36.0°C) was associated with decreased risk of delirium in post-cardiac arrest patients.[32] There was no randomized trial to investigate the effect of intraoperative target temperature management on the incidence of ED.

In line with previous studies, the present study reconfirmed that age, preoperative MCI, duration of surgery, site of surgery, and pain intensity were associated with ED.[5-8]

Our study also had some limitations. First, this was a secondary analysis of an observational study, which might limit the generality of the result. Second, we used the axillary temperature one day before surgery as a baseline reference but not the temperature on surgery day. This was because the axillary temperature on surgery day morning would be missed in most patients. However, this limitation might raise up some concerns. Body temperature has diurnal rhythm and the temperature right before anesthesia induction may be ideal for baseline reference.[33] Third, the temperature was monitored at two different sites. There was evidence which showed that axillary temperature was comparable with esophageal temperature in representing core temperature.[34] To be practical, it's not easy to obtain esophageal temperature in awake patients before anesthesia. The axillary or tympanic temperature may be considered as an alternative approach to access the baseline reference. Fourth, we did not collect the information about long-term medications (i.e., benzodiazepines and statins) which might be associated with delirium. Most older patients take long-term medications to overcome comorbidities such as hyperlipidemia and coronary artery disease. Thus, it will be interesting to investigate if these medications are associated with ED. Fifth, we did not monitor neuromuscular block status. A previous study showed that both residual neuromuscular blockade and lower body temperature were associated with increased risk of hypoactive emergence.[12] We provided the dosage of neuromuscular blockade agents which showed no statistical significance between the two groups. But there was a potential risk that hypothermia may decrease the elimination of neuromuscular blockade agents and increased the risk of ED.

In conclusion, we found that intraoperative hypothermia was common in elderly surgical patients. Hypothermia, defined as either absolute hypothermia (<35.5°C) or relative hypothermia (decrement from baseline temperature >1.0°C), was associated with increased risk of ED. The cumulative duration of absolute and relative hypothermia were also associated with increased risk of ED. Relative hyperthermia (increment from baseline temperature >0.5°C) was associated with decreased risk of ED.

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Conflicts of interest

None.

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