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Association between serum chemokines levels and delayed neurocognitive recovery after non-cardiac surgery in elderly patients: a nested case–control study

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Abstract

Background Perioperative neurocognitive disorders encompass delayed neurocognitive recovery (dNCR). Emerging evidence suggests that chemokines play a crucial role in the pathogenesis of various cognitive impairment diseases. However, the association between chemokines and dNCR remains unclear. Therefore, we aimed to investigate the relationship between serum chemokine levels and dNCR in elderly patients undergoing non-cardiac surgery.

Methods A total of 144 patients undergoing elective major non-cardiac surgery were accessed in neuropsychological testing 1 day prior to and 1 week following the surgery. Blood samples were collected before the initiation of anesthesia and one hour following the cessation of anesthesia. We employed a retrospective nested case–control study design, utilizing one control per dNCR case. Matching criteria included age (± 5 years), duration of surgery (± 90 min), and baseline MMSE score (± 3). We compared the serum levels of CCL2, CCL5, CCL11, and CXCL8 between the matched dNCR and non-dNCR groups.

Results dNCR was observed in 31.25% (45 of 144) of the patients seven days post-surgery, resulting in a final matched sample size of 21 pairs. In the preoperative comparison, the serum concentration of CCL11 was significantly higher in the matched dNCR group compared to the matched non-dNCR group ($P = 0.039$). In the postoperative comparison, the CCL5 concentration was significantly lower in the dNCR than in the non-dNCR group ($P = 0.030$). When comparing the differences between postoperative and preoperative levels, the absolute change in CCL11 was significantly greater in the dNCR group compared to the non-dNCR group ($P = 0.046$). Additionally, the postoperative-to-preoperative ratios of CCL5 and CCL11 in the dNCR group were both significantly lower than those in the non-dNCR group ($P = 0.046$, $P = 0.005$). There were no significant differences in CCL2 or CXCL8 levels between the two matched groups.

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Conclusions Serum levels of CCL 5 and CCL 11 significantly decreased in elderly patients with dNCR following non-cardiac surgery, which may contribute to the identification of patients at high risk for dNCR.

Trial registration This study was registered on chictr.org.cn (ChiCTR1800014473, 16/01/2018).

Keywords Postoperative cognitive complications, Cognitive dysfunction, Chemokines, Aged, Inflammation, Surgery

Background

Perioperative neurocognitive disorder (PND) is among the most common postoperative complications, particularly in elderly patients, and includes postoperative delirium, delayed neurocognitive recovery (dNCR), mild neurocognitive disorders, and major neurocognitive disorders (Evered et al. 2018a, b). dNCR, also referred to as early postoperative cognitive dysfunction (POCD), is defined as cognitive impairment occurring 1 to 4 weeks after surgery (Evered et al. 2018a, b), and has been associated with loss of independence, decreased quality of life and increased risk of mortality (Evered et al. 2018a, b; Evered and Silbert 2018; Mashour et al. 2015; Moller et al. 1998; Paredes et al. 2016). Despite the identification of several risk factors (Androsova et al. 2015; Evered et al. 2016; Han et al. 2019; Silbert et al. 2015; Zhang et al. 2023; Zhang et al. 2021), the underlying mechanisms of dNCR remain uncertain.

Chemokines are cytokines that regulate the directional migration of cells and exert their effects through chemokine receptors (Yoshie et al. 2001). These molecules play a crucial role in the nervous system (Liu et al. 2014a), including mediating neuroinflammation (Chui and Dorovini-Zis 2010; Roth-Isigkeit et al. 1999), promoting neurodevelopment, and increasing the generation of new neurons in the hippocampus (Liu et al. 2014b). The mechanisms underlying cognitive impairment are complex, involving both neuroinflammation (Hovens et al. 2014; Sanders and Avidan 2013) and the defensive and compensatory responses of the nervous system (Buvanendran et al. 2006; Cibelli et al. 2010). Glumac et al. (2021) found that preoperative administration of corticosteroids appears to reduce the severity and incidence of POCD for an extended period following surgery by attenuating the inflammatory response triggered by the surgical procedure. Furthermore, another study by Glumac (Glumac et al. 2019) demonstrated a close relationship between postoperative delirium and dNCR, suggesting that delirium may serve as a harbinger of dNCR, which has far greater implications for patient health and the healthcare system than delirium alone. These findings indicate that chemokines may play a significant role in the pathogenesis of dNCR.

The function of the nervous system is closely associated with chemokine CC motif ligands (CCL) 2, CCL5, CCL11, and chemokine CXC motif ligand 8 (CXCL8), among the approximately 50 chemokines identified in the human body. Studies have demonstrated that Alzheimer's disease (AD) lesions exhibit high expression levels of inflammatory factors such as CCL2 and CXCL8 (Veryard et al. 2013; Zhou et al. 2023). Additionally, serum CCL5 levels in patients with AD are significantly elevated compared to controls (Ignatov et al. 2006), while serum CCL11 levels are increased in animal models of neuroinflammation (Roy-O'Reilly et al. 2017; Shein et al. 2014; Villeda et al. 2011). Furthermore, the levels of serum chemokines in patients experiencing delirium after cardiac surgery have been reported to be elevated (Rudolph et al. 2008). Conversely, some studies have indicated that serum CCL5 levels in AD patients may decrease (Haskins et al. 2016), and the release of CCL11 from cells is inhibited following ischemic stroke (Garcia-Zepeda et al. 1996). These findings suggest that CCL2, CCL5, CCL11, and CXCL8 may significantly influence cognitive impairment; however, the results are inconsistent, and there is a notable lack of clinical studies investigating the relationship between chemokines and dNCR.

As a novel clinical investigation, this study aimed to explore the relationship between serum chemokine levels and dNCR in elderly patients undergoing non-cardiac surgery. We assessed cognitive function in the participants approximately 1 week post-surgery to determine the presence of dNCR. We hypothesized that serum levels of CCL2, CCL5, CCL11, and CXCL8 may be associated with dNCR, thereby enhancing our understanding of the relationship between chemokines and perioperative neurocognitive disorders.

Methods

Study design

This trial was registered at http://www.chictr.org.cn (registration number: ChiCTR1800014473; principal investigator: J.-L.C.; registration date: January 16, 2018). We conducted a retrospective nested case–control study utilizing participants from a prospective cohort, as previously registered before patient enrollment at https://www.clinicaltrials.gov (clinical trial registration number: NCT02992600; principal investigator: J.-L.C.; registration date: December 14, 2016). The study received approval from the clinical research ethics committee of the Affiliated Hospital of Xuzhou Medical University,

Jiangsu, China (Certification No. XYFY2017-KL004 - 02, approved date: February 23, 2017), and written informed consent was obtained from all participants. This manuscript complies with all applicable STROBE guidelines.

Subject enrollment

Elderly patients aged 60 to 85 years referred for elective major non-cardiac and non-neurological surgery under general anesthesia, with an anticipated hospital stay of 5 days or longer, were evaluated at the Affiliated Hospital of Xuzhou Medical University from March 2016 to December 2017. A flow chart detailing the patient enrollment process is presented in Fig. 1.

Other inclusion criteria included American Society of Anesthesiologists (ASA) class I or II and Geriatric Depression Scale grade I or II. Patients were excluded if they met any of the following criteria: (1) the presence of mental or neurodegenerative diseases; (2) a history of severe trauma or surgery within the past year; (3) severe visual, auditory, or motor deficits; (4) a history of substance abuse, including psychotropic drugs; (5) significant organ dysfunction; (6) prior neuropsychological testing; (7) difficulty performing tests (including severe visual or auditory disorders); and (8) a baseline Mini-Mental State Examination (MMSE) score less than 24 points, less than 20 points for participants with only an elementary school education, or less than 17 points for those who had not attended school. Patients were also excluded after enrollment if they were non-compliant with the study protocol, if their intraoperative systolic blood pressure fell below 80 mmHg, or if there was a decrease of more than 30% from baseline blood pressure for longer than 5 min.

Anesthesia protocols

Anesthesia care was standardized in accordance with American Society of Anesthesiology guidelines and hospital protocol. During the procedure, heart rate, blood pressure, peripheral oxygen saturation, electrocardiogram, end-tidal carbon dioxide ($P_{ET}CO_2$), and spectral entropy indices were continuously monitored in the operating room.

Patients received midazolam for anxiety reduction, followed by etomidate, cisatracurium, and fentanyl for anesthesia induction. Approximately 5 min after the administration of these agents, patients were intubated and ventilated to maintain a $P_{ET}CO_2$ of 35 ± 5 mmHg. Anesthesia was maintained using inhaled sevoflurane, propofol, intravenous remifentanil, and cisatracurium. During the maintenance phase, the bispectral index

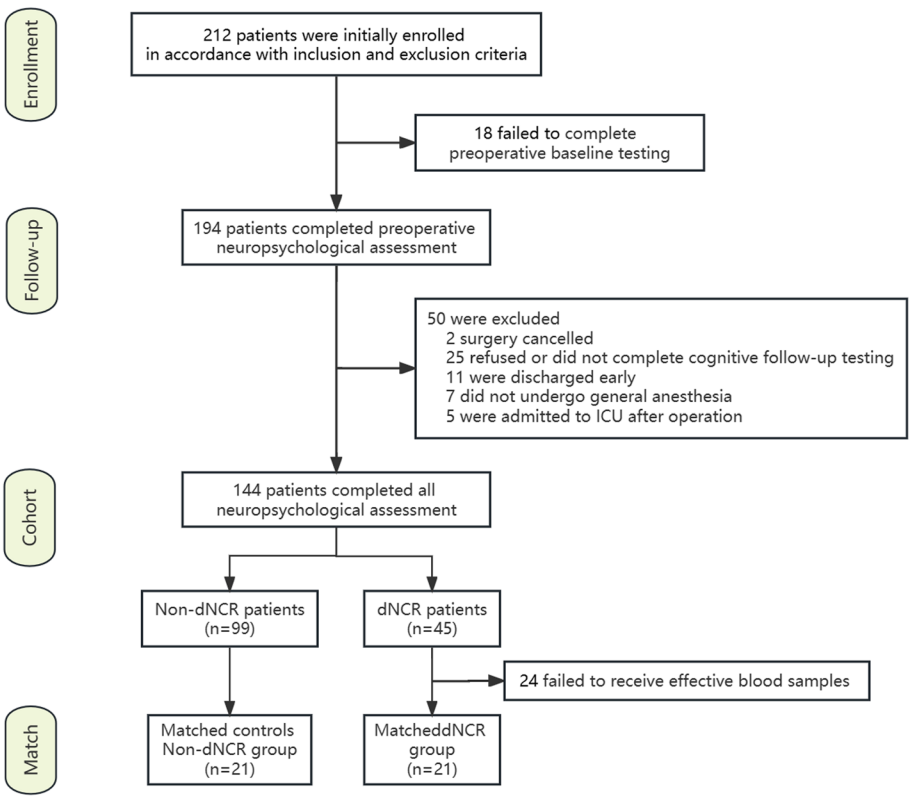

Fig. 1 Enrollment flow chart for the study population

(BIS) was kept between 40 and 60. None of the enrolled patients received epidural anesthesia; they were transferred to the post-anesthesia care unit (PACU) following surgery, where they were administered neostigmine and flumazenil. All aspects of clinical care were meticulously documented in each patient's electronic medical record.

Neuropsychological testing

Each enrolled participant underwent a standard battery of neuropsychological tests in a quiet hospital office setting, conducted 1 day before surgery (baseline) and again 5 to 10 days (mean of 7 days) postoperatively. This neuropsychological testing battery was designed to assess memory, psychomotor speed and dexterity, physical motor speed, attentional capacity, and perceptual-spatial functioning. The tests were selected based on recommendations from the International Studies of Postoperative Cognitive Dysfunction (ISPOCD 1 and 2) (Moller et al. 1998; Rasmussen et al. 2001, 2005). The specific tests administered included the Short Story Module of the Randt Memory Test (immediate and delayed recall), Verbal Fluency Test, Trail Making Test (Part A), Digit Symbol Subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS, Chinese edition), Digit Span (forward and backward) Subtests of the WAIS, Finger-tapping task, Grooved Pegboard Test (for both dominant and nondominant hands), and the Block Test. The cognitive domains assessed by these tests are summarized in Table 1.

Researchers underwent extensive training in the administration of tests and relevant interview techniques, adhering to a strict and standardized written protocol to minimize inter-examiner variability. Cognitive assessments for each patient were conducted by the same examiner and were repeated after surgery.

Control group

To mitigate the risk of misinterpreting the identification of dNCP due to practice effects and natural variation in repeated cognitive test performances (Jacobson and Truax 1991), a non-surgical control group was established. In this study, 30 age- and sex-matched healthy volunteers were recruited from the friends and family members of the enrolled patients, adhering to the same exclusion criteria. These volunteers underwent the same neuropsychological testing administered by the same researchers and at the same time intervals as the trial participants, but they had not undergone any surgical procedures or anesthesia in the preceding year.

Calculation of dNCR

The dNCR was defined in accordance with the criteria established by the ISPOCD 1 study (Moller et al. 1998; Rasmussen et al. 2001, 2005). For each participant, we evaluated the change in baseline test scores compared to postoperative scores. We calculated the change for each individual, subtracted the mean difference observed in the control group, and then divided the result by the standard deviation (SD) of the control group's difference to derive a Z-score for nine individual test outcomes. dNCR cases were identified as those exhibiting a Z-score of ≤ -1.96 on at least two distinct tests, representing 20% of the neuropsychological assessments conducted.

Biological measurements

Blood samples were collected from patients immediately before the initiation of anesthesia and 1 h after its completion. These samples were placed in serum separator (SST) tubes and promptly centrifuged at 3000 ×g for 10 min. The resulting serum samples were stored at −80℃ until further biological analysis.

Table 1 Cognitive domains and neuropsychological tests

Domain	Tests
Memory (short-term, intermediate-term)	The Short Story module of the Randt Memory (immediate, delayed recall)
Psychomotor speed	Trail Making Test (Part A)
	Digit Symbol Subtest of the Wechsler Adult Intelligence Scale-Revised (Chinese edition)
Manual dexterity	Grooved Pegboard Test (dominant and nondominant)
Attention and concentration	Digit Span (forward and backward) Subtests of the Wechsler Adult Intelligence Scale-Revised (Chinese edition)
Speed and flexibility of verbal thought process	The Verbal Fluency Test
Motor domain	Finger tapping
Perceptual-spatial function	Block subtest of the Wechsler Adult Intelligence Scale-Revised (Chinese edition)

Serum chemokines were assessed using high-throughput quantitative detection via a solid-phase chip, employing customized test kits (QAH-CUST- 12; RayBiotech, USA). This methodology utilizes multiple sandwich enzyme-linked immunosorbent assays (ELISA) to simultaneously quantify a range of cytokines, leveraging the high specificity and sensitivity of ELISA alongside the throughput advantages of the chip technology. A minimal volume of serum was required to concurrently measure the concentrations of four chemokines: CCL2, CCL5, CCL11, and CXCL8.

Nested case–control group

After approximately 1 week of follow-up, matched controls (one control per dNCR case) were randomly selected from the non-dNCR group by an independent blinded researcher. The matching criteria employed in this nested case–control study design included age (± 5 years), duration of surgery (± 90 min), and baseline MMSE score (± 3 points).

Statistical analysis

The normality of the continuous variables was assessed using the Shapiro–Wilk test. Normally distributed continuous variables are presented as means with SD and were compared using the Student *t*-test. Non-normally distributed continuous variables are reported as medians with interquartile ranges (IQR) and were compared using the Mann–Whitney *U* test. Categorical variables are expressed as counts with percentages of the total (%), and comparisons were made using the χ^2 test or Fisher's exact test as appropriate. All analyses accounted for correlation within matched case–control sets when applicable.

Z-score normalization of the original data was performed to elucidate the changes in postoperative markers, using the non-dNCR group as a reference (mean = 0, SD = 1). Student's *t*-tests were conducted to compare the *z*-scores of various markers.

All hypothesis testing was two-tailed, with a *P* value of < 0.05 denoting statistical significance. Statistical analyses were conducted using SPSS (version 23.0, IBM, USA).

Results

Study participants

The patient enrollment flow for this study is illustrated in Fig. 1. Among the thousands of patients assessed for eligibility, 212 were initially enrolled based on the established inclusion and exclusion criteria and expressed willingness to participate during the preoperative interview. However, 18 patients did not complete baseline neuropsychological testing, resulting in a final enrollment of 194 patients. During the postoperative follow-up, 2 patients canceled their surgeries, 25 patients either refused or were unable to complete cognitive follow-up testing, 11 were lost to follow-up due to earlier discharge, 7 did not undergo general anesthesia, and 5 were admitted to the intensive care unit postoperatively. Consequently, a total of 50 patients were excluded from subsequent data collection, leaving data from 144 patients for analysis in this cohort study.

dNCR cases were identified in 45 of the 144 surgical patients (31.25%; 95% confidence interval (CI), 23.6 to 38.9%) one week postoperatively. Among these, blood samples were available for only 21 patients, which constituted the matched dNCR group. Subsequently, 21 matched controls (one control per dNCR case) were selected from the non-dNCR patients based on age, duration of surgery, and baseline MMSE score, creating a nested case–control study. The final cohort for laboratory investigation comprised 21 confirmed dNCR cases and 21 matched controls. The demographic and clinical characteristics of this cohort are presented in Table 2 (Additional file 1: Tables S1 and S2), with no significant differences observed between the matched dNCR and non-dNCR groups (Table 2).

Cognitive outcomes

The results of all neuropsychological tests for the matched groups at baseline and at the 1-week follow-up are presented in Additional file 1: Tables S3 and S4. There were no significant differences in individual neuropsychological test scores at baseline among the 21 pairs. However, at 1-week follow-up, matched patients with dNCR exhibited poorer performance primarily in the delayed recall of the Short Story Module of the Randt Memory Test, the nondominant hand scores of the Grooved Pegboard Test, the Digit Symbol Subtest of WAIS, and the Digit Span Subtests (forward and backward) of the WAIS.

The control group comprised 30 age- and sex-matched volunteers to mitigate bias in neuropsychological testing, with their results at baseline and at 1-week follow-up detailed in Additional file 1: Table S5.

Chemokines and dNCR

At baseline, matched patients who developed dNCR had significantly higher serum CCL11 concentrations compared to those without dNCR (30.59 (29.93) pg/ml vs 22.20 (22.42) pg/ml; normalized scores: 1.26 (0.51) vs 1.02 (0.71); *z*-scores: 0.34 (0.71) vs 0.0 (1.0); $P = 0.039$). However, no significant differences were observed in CCL2, CCL5, and CXCL8 levels between the matched dNCR and non-dNCR groups (Table 3).

This table summarizes the comparisons of chemokine markers at baseline. Raw scores were log-normalized due to data skewness. Normalized scores were standardized

to a mean of 0 and an SD of 1 (z-scores) within the matched non-dNCR group. Therefore, the marker z-scores for the matched non-dNCR group reflect a mean of 0 with an SD of 1.

At 1 h following the conclusion of anesthesia, matched patients with dNCR exhibited significantly lower serum CCL5 concentrations compared to those without dNCR (913.50 (135.08) pg/ml vs 996.25 (140.62) pg/ml; normalized scores: 2.96 (0.07) vs 2.99 (0.06); z-scores: −0.56 (1.11) vs 0.0 (1.0); $P = 0.030$). However, there were no significant differences in the levels of CCL2, CCL11, and CXCL8 between the two matched groups (Table 4).

This table summarizes the comparisons of chemokine markers at 1 h postoperatively. Raw scores were log-normalized due to data skewness. Normalized scores were standardized to a mean of 0 and an SD of 1 (z-scores) within the matched non-dNCR group. Therefore, the marker z-scores for the matched non-dNCR group reflect a mean of 0 with an SD of 1.

Table 2 Demographic and clinical characteristics of matched groups

	Matched dNCR group ($n = 21$)	**Matched non-dNCR group ($n = 21$)**	***P* value**
Age (years), mean (SD)	68.62 (6.599)	68.57 (5.715)	0.980
Female sex, *n* (%)	4 (19.048)	9 (42.857)	0.090
BMI (kg m^{-2}), mean (SD)	24.75 (4.107)	23.55 (2.674)	0.271
Education (years), mean (SD)	7.29 (3.862)	7.86 (3.351)	0.611
Type of surgery, *n* (%)			
Stomach enterochirurgia	11 (52.381)	11 (52.381)	1.000
Osteoarticular surgery	3 (14.286)	3 (14.286)	
Urinary surgery	7 (33.333)	7 (33.333)	
Duration of surgery (min), mean (SD)	209.52 (70.833)	203.81 (60.661)	0.780
Duration of anesthesia (min), mean (SD)	240.95 (72.174)	238.57 (61.505)	0.909
Preoperative MMSE score, mean (SD)	25.86 (2.670)	26.71 (2.452)	0.285

Abbreviations: *BMI* body mass index, *MMSE* Mini-Mental State Examination, *SD* standard deviation

Table 3 Preoperative chemokine markers in matched groups

	Raw (pg/ml)		**Normalized**		**Marker *Z*-scores**		
	Matched dNCR	**Matched non-dNCR**	**Matched dNCR**	**Matched non-dNCR**	**Matched dNCR**	**Matched non-dNCR**	***P* value**
CCL2	65.89 (24.98)	65.24 (23.07)	1.79 (0.18)	1.79 (0.17)	− 0.02 (1.06)	0.0 (1.0)	0.926
CCL5	983.91 (159.12)	1039.91 (242.30)	2.99 (0.07)	3.00 (0.11)	− 0.12 (0.68)	0.0 (1.0)	0.422
CCL11	30.59 (29.93)	22.20 (22.42)	1.26 (0.51)	1.02 (0.71)	0.34 (0.71)	0.0 (1.0)	0.039*
CXCL8	3.45 (1.790)	4.06 (4.43)	0.47 (0.26)	0.46 (0.33)	0.04 (0.79)	0.0 (1.0)	0.828

Data are presented as mean (SD)

* $P < 0.05$, paired samples t-test

Table 4 Postoperative chemokine markers in matched groups

	Raw (pg/ml)		**Normalized**		**Marker *Z*-scores**		
	Matched dNCR	**Matched non-dNCR**	**Matched dNCR**	**Matched non-dNCR**	**Matched dNCR**	**Matched non-dNCR**	***P* value**
CCL2	84.61 (80.96)	84.62 (86.88)	1.72 (0.45)	1.77 (0.37)	− 0.14 (1.22)	0.0 (1.0)	0.611
CCL5	913.50 (135.08)	996.25 (140.62)	2.96 (0.07)	2.99 (0.06)	− 0.56 (1.11)	0.0 (1.0)	0.030*
CCL11	14.15 (20.36)	16.97 (18.45)	0.92 (0.43)	0.88 (0.68)	0.06 (0.63)	0.0 (1.0)	0.662
CXCL8	5.73 (5.97)	4.41 (3.24)	0.53 (0.34)	0.58 (0.38)	− 0.13 (0.9)	0.0 (1.0)	0.513

Data are presented as mean (SD)

* $P < 0.05$, paired samples t-test

In the matched dNCR cases, postoperative serum concentrations of CCL5 decreased significantly compared to the preoperative levels (913.50 (135.08) pg/ml vs 983.91 (159.12) pg/ml; normalized scores: 2.96 (0.07) vs 2.99 (0.07); *z*-scores: −0.48 (0.95) vs 0.0 (1.0); $P = 0.031$). Similarly, postoperative serum concentrations of CCL11 were significantly lower than preoperative levels (14.15 (20.36) pg/ml vs 30.59 (29.93) pg/ml; normalized scores: 0.92 (0.43) vs 1.26 (0.51); *z*-scores: −0.66 (0.85) vs 0.0 (1.0); $P = 0.002$). Conversely, serum levels of CCL2 and CXCL8 did not demonstrate significant changes following surgery (Table 5 and Additional file 1: Fig. S1).

This table summarizes the comparisons of preoperative and postoperative chemokine markers in the matched dNCR group. Raw scores were log-normalized due to data skewness. Normalized scores were standardized to a mean of 0 and an SD of 1 (*z*-scores) within the matched non-dNCR group. Therefore, the marker *z*-scores for the matched non-dNCR group reflect a mean of 0 with an SD of 1.

In the matched non-dNCR controls, no significant changes were observed in the serum concentrations of CCL2, CCL5, CCL11, and CXCL8 between the preoperative and postoperative assessments (Table 6 and Additional file 1: Fig. S2).

This table summarizes the comparisons of preoperative and postoperative chemokine markers in the matched non-dNCR group. Raw scores were log-normalized due to data skewness. Normalized scores were standardized to a mean of 0 and an SD of 1 (*z*-scores) within the matched non-dNCR group. Therefore, the marker *z*-scores for the matched non-dNCR group reflect a mean of 0 with an SD of 1.

Regarding the difference (D) in postoperative and preoperative chemokine levels, the change in serum CCL11 concentration was significantly smaller in the dNCR pairs compared to those without dNCR (− 16.43 (24.22) pg/ml vs −5.23 (25.43) pg/ml; normalized scores: −0.34 (0.48) vs −0.12 (0.57); *z*-scores: −0.39 (0.83) vs 0.0 (1.0); $P = 0.046$). No significant differences were observed in the changes of CCL2, CCL5, or CXCL8 levels between the two matched groups (Table 7 and Additional file 1: Fig. S3).

This table summarizes the comparisons of differences between postoperative and preoperative chemokine markers in matched dNCR and non-dNCR groups. Raw scores were log-normalized due to data skewness. Normalized scores were standardized to a mean of 0 and an SD of 1 (*z*-scores) within the matched non-dNCR group. Therefore, the marker *z*-scores for the matched non-dNCR group reflect a mean of 0 with an SD of 1.

In terms of the ratio (R) of postoperative to preoperative chemokine levels, the R values for serum CCL5 and CCL11 concentrations were significantly lower in the matched dNCR group compared to the non-dNCR group (CCL5: 0.94 (0.11) vs 0.99 (0.19), *z*-scores: −0.28 (0.59)

Table 5 Preoperative and postoperative chemokine markers in matched dNCR groups

	Raw (pg/ml)		Normalized		Marker *Z*-scores		
	Pre-operative	Post-operative	Pre-operative	Post-operative	Pre-operative	Post-operative	*P* value
CCL2	65.89 (24.98)	84.61 (80.96)	1.79 (0.18)	1.72 (0.45)	0.0 (1.0)	− 0.39 (2.52)	0.481
CCL5	983.91 (159.12)	913.50 (135.08)	2.99 (0.07)	2.96 (0.07)	0.0 (1.0)	− 0.48 (0.95)	0.031*
CCL11	30.59 (29.93)	14.15 (20.36)	1.26 (0.51)	0.92 (0.43)	0.0 (1.0)	− 0.66 (0.85)	0.002*
CXCL8	3.45 (1.790)	5.73 (5.97)	0.47 (0.26)	0.53 (0.34)	0.0 (1.0)	0.23 (1.31)	0.427

Data are presented as mean (SD)

* $P < 0.05$, paired samples *t*-test

Table 6 Preoperative and postoperative chemokine markers in matched non-dNCR groups

	Raw (pg/ml)		Normalized		Marker *Z*-scores		
	Pre-operative	Post-operative	Pre-operative	Post-operative	Pre-operative	Post-operative	*P* value
CCL2	65.24 (23.07)	84.62 (86.88)	1.79 (0.17)	1.77 (0.37)	0.0 (1.0)	− 0.11 (2.18)	0.821
CCL5	1039.91 (242.30)	996.25 (140.62)	3.00 (0.11)	2.99 (0.06)	0.0 (1.0)	− 0.05 (0.55)	0.670
CCL11	22.20 (22.42)	16.97 (18.45)	1.02 (0.71)	0.88 (0.68)	0.0 (1.0)	− 0.20 (0.96)	0.342
CXCL8	4.06 (4.43)	4.41 (3.24)	0.46 (0.33)	0.58 (0.38)	0.0 (1.0)	0.38 (1.14)	0.144

Data are presented as mean (SD)

* $P < 0.05$, paired samples *t*-test

Table 7 Differences between postoperative and preoperative chemokine markers in matched groups

	Raw (pg/ml)		Normalized		Marker *Z*-scores		
	Matched dNCR	Matched non-dNCR	Matched dNCR	Matched non-dNCR	Matched dNCR	Matched non-dNCR	*P* value
CCL2	18.72 (74.09)	19.38 (86.81)	− 0.07 (0.38)	− 0.01 (0.32)	− 0.18 (1.19)	0.0 (1.0)	0.503
CCL5	− 70.41 (102.89)	− 43.66 (144.37)	− 0.03 (0.05)	− 0.01 (0.07)	− 0.30 (0.75)	0.0 (1.0)	0.083
CCL11	− 16.43 (24.22)	− 5.23 (25.43)	− 0.34 (0.48)	− 0.12 (0.57)	− 0.39 (0.83)	0.0 (1.0)	0.046*
CXCL8	0.97 (3.28)	1.67 (6.43)	0.06 (0.29)	0.13 (0.36)	− 0.20 (0.82)	0.0 (1.0)	0.282

Data are presented as mean (SD)

* $P < 0.05$, paired samples *t*-test

vs 0.0 (1.0), $P = 0.046$; CCL11: 0.85 (1.16) vs 1.64 (2.60), *z*-scores: −0.30 (0.44) vs 0.0 (1.0), $P = 0.005$). However, no significant differences in the *R* values for serum CCL2 and CXCL8 concentrations were observed between the matched dNCR and non-dNCR participants (Table 8 and Additional file 1: Fig. S4).

This table compares the ratios of postoperative to preoperative chemokine markers in matched dNCR and non-dNCR groups. Raw scores were log-normalized due to data skewness. Normalized scores were standardized to a mean of 0 and an SD of 1 (*z*-scores) within the matched non-dNCR group. Therefore, the marker *z*-scores for the matched non-dNCR group reflect a mean of 0 with an SD of 1.

Discussion

In this study of elderly patients undergoing non-cardiac surgery, we identified two chemokine markers, CCL5 and CCL11, that are associated with dNCR. The data revealed that patients who developed dNCR exhibited a greater difference between pre- and post-operative levels of CCL11, as well as lower ratios of post- to pre-operative levels of CCL5 and CCL11, than patients who did not develop dNCR. The significant decreases in serum levels of CCL5 and CCL11 levels after surgery may indicate an increased risk of dNCR, suggesting an association between chemokines and dNCR in elderly patients.

Neuroinflammation mechanisms in dNCR and the blood–brain barrier

Neuroinflammation is increasingly recognized as a key mechanism underlying dNCR (Hovens et al. 2014; Sanders and Avidan 2013). Research indicates that neuroinflammatory processes, along with subsequent nerve injuries following anesthesia or surgery procedures, can precipitate a range of behavioral, emotional, and cognitive disturbances (Severini et al. 2014).

The underlying mechanisms involve the transmission of immunologic signals from the periphery to the central nervous system (CNS) following operative injury, which triggers the release of inflammatory mediators by central system cells. Surgical trauma activates the innate immune system, resulting in the liberation of inflammatory factors that compromise endothelial cell integrity and disrupt the blood–brain barrier (BBB). This disruption facilitates the migration of peripheral inflammatory cells into the CNS (Terrando et al. 2011; Vacas et al. 2013).

Notably, the expression of proinflammatory cytokine receptors in the hippocampus—a region critical for memory consolidation and neuroplasticity—demonstrably increases after operative trauma. This sustained activation of inflammatory cells in the hippocampus may contribute to irreversible cognitive impairments (Rothwell and Hopkins 1995).

In the neuroinflammatory process described above, the impairment of BBB and alterations in its permeability

Table 8 Ratios of postoperative to preoperative chemokine markers in matched groups

	Raw		Marker Z-Scores		
	Matched dNCR	Matched non-dNCR	Matched dNCR	Matched non-dNCR	*P* value
CCL2	1.23 (1.13)	1.33 (1.48)	− 0.06 (0.77)	0.0 (1.0)	0.700
CCL5	0.94 (0.11)	0.99 (0.19)	− 0.28 (0.59)	0.0 (1.0)	0.046*
CCL11	0.85 (1.16)	1.64 (2.60)	− 0.30 (0.44)	0.0 (1.0)	0.005*
CXCL8	1.51 (1.48)	2.06 (2.70)	− 0.20 (0.55)	0.0 (1.0)	0.104

Data are presented as mean (SD)

* $P < 0.05$, paired samples *t*-test

may play a crucial role in the pathogenesis of dNCR (Terrando et al. 2011). Specifically, changes in BBB integrity can lead to peripheral cytokine levels becoming indicative of their concentrations in the CNS to a certain extent (Sun et al. 2003).

CCL5, CCL11 and cognitive impairment

CCL5, also known as regulated upon activation, normal T cell expressed and secreted (RANTES), is produced by central endothelial cells, glial cells, and neurons, as well as by peripheral inflammatory cells, including natural killer (NK) cells and T lymphocytes. CCL5 has been shown to promote cell survival and modulate microglia activity in the brain (Azizi et al. 2014). Increased expression of CCL5 may help mitigate immunopathological damage and support normal cognitive function (Terrando et al. 2011).

Research indicates that CCL5 plays a role in preventing amyloid-related cell death in AD, with serum levels of CCL5 in AD patients being significantly elevated compared to those in control subjects (Ignatov et al. 2006). However, our study found that serum CCL5 levels in patients with dNCR were significantly lower than those in the non-dNCR group.

Several factors may contribute to these divergent findings. Surgical procedures, anesthesia, and cancer can affect the peripheral immune system, potentially leading to the inhibition of CCL5-secreting cells, such as microglia, in dNCR patients, which would result in decreased CCL5 levels. Additionally, since CCL5 levels were assessed using peripheral blood samples, it is possible that immune cells in peripheral blood exert a greater influence on CCL5 levels than those in the CNS.

CCL11, also known as eosinophil activation chemokine- 1 (Eotaxin- 1), plays a significant role in the pathogenesis of various neurological disorders by enhancing neuroinflammation and neurotoxicity of microglia (Azizi et al. 2014). This chemokine, produced by multiple cell types including lymphocytes, astrocytes, monocytes, endothelial cells, and neurons (Fryer et al. 2006; Parajuli et al. 2015), has been shown to inhibit the development of the nervous system (Erickson et al. 2014; Targowski et al. 2005).

Research indicates that CCL11 can cross the BBB, thereby influencing microglia activity, and accelerating the progression of neurological diseases (Erickson et al. 2014; Targowski et al. 2005). Villeda et al. (2011) reported that elevated blood levels of CCL11 in aging negatively regulate adult hippocampal neurogenesis, contributing to cognitive decline. Furthermore, increased circulating levels of CCL11 have been associated with neuroinflammation (Ignatov et al. 2006; Roy-O'Reilly et al. 2017).

In our study, we found that patients with high preoperative serum CCL11 levels were more likely to develop dNCR. In contrast, postoperative serum CCL11 levels in patients with dNCR significantly decreased compared to those without dNCR. This phenomenon may be attributed to the bidirectional transportation of CCL11 across the BBB, allowing CCL11 from the bloodstream to access various brain regions beyond the neurogenic niche (Erickson et al. 2014). Notably, the uptake of CCL11 from the blood to the brain occurs rapidly, resulting in increased accumulation within the CNS, whereas the transport of CCL11 from the brain to the blood is slower and often reaches saturation, leading to decreased serum levels.

Another contributing factor may be the different degrees of cerebral ischemia and hypoxia induced by anesthesia or surgery, which can lead to significant systemic immunosuppression. Consequently, the release of CCL11 may be inhibited, resulting in lower circulating levels. Similar conclusions have been drawn in studies focused on ischemic stroke (Garcia-Zepeda et al. 1996).

CCL2, CXCL8 and cognitive impairment

CCL2, also known as monocyte chemoattractant protein- 1 (MCP- 1), plays a critical role in neuroinflammation associated with various neurodegenerative diseases (Huang et al. 2000; Stuart and Baune 2014; Westin et al. 2012). It is primarily secreted by periphery macrophages, as well as by astrocytes and microglia in the brain, with some contribution from endothelial cells. Following CNS injury and inflammation, the upregulation of CCL2 and its receptor, CCR2, promotes the infiltration of mononuclear macrophages into brain tissue.

Research indicates that peripheral blood levels of CCL2 and CCR2 are correlated with cognitive impairment and depression (Deshmane et al. 2009; Pae et al. 2004; Pola et al. 2004) and may influence the progression from mild cognitive impairment to dementia (Porcellini et al. 2013). Furthermore, CCL2 has been shown to facilitate the formation of amyloid β-protein (Aβ) oligomers in microglia, thereby accelerating neurocognitive dysfunction by influencing Aβ seeding in the brain (Kiyota et al. 2009).

CXCL8, also known as interleukin (IL)− 8, is implicated as an important mediator of neuronal apoptosis in AD (Stuart and Baune 2014; Westin et al. 2012). This chemokine is primarily produced by monocytes, endothelial cells, hepatocytes, and fibroblasts in the periphery, as well as by monocytes, microglia, astrocytes, and neurons in the brain.

CXCL8 facilitates the immune inflammatory response induced by Aβ by mediating intercellular communication. Notably, microglia in the presence of Aβ exhibit increased secretion of proinflammatory cytokines in

response to CXCL8 (Li et al. 2009). Studies have shown that serum inflammatory factors, including TNF-α and CXCL8, are elevated in elderly patients undergoing surgical procedures (Green et al. 2015) and in animal models of cognitive impairment (Tan et al. 2014).

In contrast, the present study did not identify statistically significant differences in CCL2 and CXCL8 levels between the two matched groups, which is inconsistent with findings reported in previous research. Several factors may contribute to this discrepancy. First, the pathogenesis of dNCR may be unrelated or only weakly associated with CCL2 and CXCL8. Second, changes in serum levels of CCL2 and CXCL8 may not accurately reflect their CNS levels. Third, the small sample size may have been insufficient to adequately reveal the relationship between serum CCL2, CXCL8, and dNCR. Finally, the limited number of blood collection time points may not have aligned with the critical intervals for assessing preoperative and postoperative differences in serum CCL2 and CXCL8 levels.

In conclusion, our findings underscore the translational value of serum levels of CCL5 and CCL11 as potential biomarkers for identifying elderly patients at high risk for dNCR following non-cardiac surgery. This identification may enhance preoperative assessments and allow for tailored interventions designed to mitigate the risk of cognitive decline. Future research should focus on elucidating the underlying mechanisms by which CCL5 and CCL11 contribute to dNCR. Longitudinal studies are also warranted to explore the roles of these chemokines in the progression of neuroinflammation and cognitive impairment. Furthermore, investigating therapeutic interventions targeting these chemokines could yield significant insights into strategies for preventing dNCR in vulnerable populations.

Advantages and limitations

The present study benefits from the utilization of a neuropsychological test battery, as established in the ISPOCD1 study, aligning with recent efforts to standardize terminology for research on cognitive changes following anesthesia and surgery (Evered et al. 2018a, b). This test battery encompasses five dimensions with nine subscales, effectively covering the cognitive domains commonly affected postoperatively. Moreover, our study included a well-matched cohort of non-surgical subjects to mitigate potential bias in neuropsychological testing. Notably, blood-based assessments, compared to cerebrospinal fluid examinations, are less invasive and more readily accepted by patients, enhancing the feasibility of the clinical trial.

The trial employed a nested case–control study design, which effectively balanced the basic characteristics of the participants and minimized the influence of confounding variables on results. This approach offers several advantages over traditional case–control studies and full cohort designs (Ernster 1994). First, nested case–control studies can achieve substantial reductions in costs and resource expenditures associated with data collection and analysis, with only a modest decrease in statistical efficiency. Second, because subjects in both study groups originate from the same cohort, the design reduces selection bias in effect estimation and enhances comparability. Third, as blood samples were obtained prior to the diagnosis of dNCR, any observed association between chemokines and dNCR is chronologically consistent with the causal inference. This temporal alignment also minimizes recall bias, thereby strengthening the credibility of causal associations.

The current study has several limitations that warrant consideration. First, it was a single-center investigation with a relatively small sample size. Due to the scarcity of clinical research exploring the relationship between chemokines and dNCR, we were unable to derive an appropriate sample size from existing literature. Although a nested case–control design was employed to address the sample size limitations in this trial, multicenter studies with larger cohorts are essential to substantiate the association between serum chemokine levels and dNCR. Second, the analysis focused solely on a single acute time point post-surgery, which may not adequately capture the variations in preoperative and postoperative chemokines levels, potentially affecting our assessment of their relationship with dNCR. Third, we conducted follow-up assessments only seven days postoperatively, limiting our ability to evaluate long-term postoperative cognitive decline and the potential association with chemokines in later stages. Finally, several confounding factors that could influence postoperative cognitive function were not incorporated into our study design. These include the specific use of midazolam in the anesthesia protocol, variations in non-cardiac surgical procedures, the impact of tumors on immunity responses, the administration of specific medications during the observation period, and the dosage of intraoperative analgesics and postoperative analgesia protocol. Future studies should carefully consider these variables to enhance our understanding of the mechanisms underlying postoperative cognitive complications.

Conclusions

Our findings indicate that elderly patients with dNCR exhibit significantly decreased serum levels of CCL5 and CCL11 following general anesthesia for non-cardiac surgery. These results may facilitate the identification of patients at high risk for dNCR and encourage

future clinical investigations aimed at elucidating the underlying mechanisms of this condition.

Abbreviations

Aβ	Amyloid β-protein
AD	Alzheimer's disease
ASA	American Society of Anesthesiologists
BBB	Blood-brain barrier
BIS	Bispectral index
CCL	Chemokine CC motif ligand
CI	Confidence interval
CNS	Central nervous system
CXCL	Chemokine CXC motif ligand
D	Difference
ELISA	Enzyme-linked immunosorbent assay
Eotaxin- 1	Eosinophil activation chemokine- 1
IL	Interleukin
ISPOCD	International Studies of Postoperative Cognitive Dysfunction
MCP	Monocyte chemoattractant protein
MMSE	Mini-Mental State Examination
NK	Natural killer
PACU	Post-anesthesia care unit
PND	Perioperative neurocognitive disorder
POCD	Postoperative cognitive dysfunction
R	Ratio
RANTES	Regulated upon activation normal T cell expressed and secreted
TNF-α	Tumor necrosis factor-α
WAIS	Wechsler Adult Intelligence Scale-Revised
BMI	Body mass index
MMSE	Mini-Mental State Examination
SD	Standard deviation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13741-025-00523-x.

Additional file 1: Table S1. Demographic and Clinical Characteristics of the dNCR Cohort. Table S2. Demographic and Clinical Characteristics of the non-dNCR Cohort. Table S3. Baseline Neuropsychological Test Results in Matched Groups. Table S4. Neuropsychological Test Results at 1-Week Follow-up in Matched Groups. Table S5. Neuropsychological Test Results of the Control Group. Figure S1. Preoperative and Postoperative Chemokine Markers in Matched dNCR Groups. Figure S2. Preoperative and Postoperative Chemokine Markers in Matched non-dNCR Groups. Figure S3. Differences Between Postoperative and Preoperative Chemokine Markers in Matched Groups. Figure S4. Ratios of Postoperative to Preoperative Chemokine Markers in Matched Groups.

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Authors' contributions
C.J.L., H.Y.: These authors designed the study, critically reviewed the manuscript, and are accountable for the work. H.L., D.M.M.: These authors designed and conducted the study; collected, analyzed and interpreted the data; were major contributors in writing the manuscript and critically reviewed the manuscript. They are accountable for the work. D.K., S.Q.C., Z.Z.F., L.H.: These authors helped in the design and conduct of the study, collection of data, and critical review of the manuscript. All authors read and approved the final manuscript.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was approved by the clinical research ethics committee of the Affiliated Hospital of Xuzhou Medical University, Jiangsu, China (Certification No. XYFY2017-KL004 - 02, approved date: February 23, 2017), and written informed consent was obtained from all subjects participating in the trial. All experiments were performed in accordance with relevant guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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