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ORIGINAL RESEARCH

Association Between Preoperative Lymphocyte-to-Monocyte Ratio and Occurrence of Postoperative Cognitive Dysfunction: A Prospective Cohort Study

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Purpose: Postoperative cognitive dysfunction (POCD) is a common postoperative complication. Studies have reported that lymphocyte-to-monocyte ratio (LMR) was a predictor of many diseases associated with inflammation. However, further examination of the relationship between preoperative LMR and POCD is needed. We aimed to investigate the association between POCD and preoperative LMR levels to examine the potential of LMR to predict POCD.

Patients and Methods: This was a prospective cohort study that included patients who underwent elective major abdominal surgery at our hospital between January 2019 and January 2022. Multivariate logistic regression analysis was used to analyze the effects of preoperative LMR on POCD development. The optimal threshold of preoperative LMR for predicting POCD was determined by receiver operating characteristic (ROC) approach. A subgroup analysis was performed according to age, sex, type of surgery and hypertension.

Results: Of 964 patients, 362 (37.6%) developed POCD. The preoperative LMR level in the Non-POCD group was higher than that in the POCD group. According to the ROC curve, a cutoff value of 3.758 of the preoperative LMR level could be used to predict POCD occurrence and the area under the curve (AUC) was 0.747 (95% CI: 0.715–0.779, $P < 0.001$). The results of the subgroup analyses were consistent with the primary ones, and no heterogeneity was observed in the subgroup analyses (P for interaction > 0.05).

Conclusion: LMR was significantly associated with the occurrence of POCD after major abdominal surgery. Preoperative low LMR levels can be used to identify patients who may be at high risk of POCD.

Keywords: postoperative cognitive dysfunction, lymphocyte-to-monocyte ratio, abdominal surgery, systemic inflammation

Introduction

With the continuous development of medical technology, surgery has become an important means of treating many diseases. However, the trauma to the surgical procedure and the use of anesthetic drugs may lead to the occurrence of postoperative cognitive dysfunction (POCD).[1,2] POCD is a common postoperative complication in patients, characterized by memory, comprehension, and attention decline or loss, which has been combined into a new term "perioperative neurocognitive disorders (PND)".[3] After non-cardiac surgery, the incidence of POCD in elderly patients ranges from 5.6% - 56.6%, even at 3 months or 1 year after surgery, it still affects approximately 10% of elderly patients.[4–6] POCD prolongs the length of hospital stay, increases hospitalization costs, reduces the quality of life, and increases perioperative and long-term mortality.[7] The mechanism of POCD is complex and is not fully understood.

Previous studies have shown that neuroinflammation resulting from surgery or anesthesia is the main contributor to the development of POCD.[8–10] Surgical models in animals showed upregulation of proinflammatory cytokines in peripheral tissues and the central nervous system.[10] In clinical studies, proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 are increased in the serum of POCD patients, regardless of the type of surgery.[11,12] These peripheral inflammatory factors enter the

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central nervous system through the blood-brain barrier disrupted by anesthesia and surgery, ultimately leading to cognitive decline.[13] Besides, cognitive decline is closely associated with abnormalities in patients' blood cell-related indicators. Studies have indicated that reduced hemoglobin levels are associated with cognitive dysfunction, and cognitive impairment is more pronounced in patients with severe anemia.[14,15] Low brain hemoglobin levels are related to hypoxia, which can lead to neuronal damage and subsequently cognitive decline.[15] Platelets play a role in hemostasis and inflammation processes. They are not only involved in wound healing but also crucial for maintaining healthy brain function through their interaction with nerve cells.[16] Research has suggested that platelet activity is an important independent predictor of the severity of cognitive impairment in these patients.[17] White blood cell (WBC) counts can reflect systemic inflammatory states in multiple diseases, and their subtypes include lymphocytes and monocytes. They are involved in regulating the body's immune and inflammatory response.[18,19] Chronic inflammation, often associated with increased activity of white blood cells, is considered a significant risk factor for cognitive decline and neurodegenerative diseases.[20–22] While lymphocyte-to-monocyte ratio (LMR) as a derived value of WBC counts has been shown to be a prognostic marker for a variety of nervous system diseases.[23–26] Lu et al did find low preoperative LMR was associated with increased risk of POCD in patients undergoing orthopedic surgery.[27] However, the study by Zhao et al in cardiovascular surgery patients found contrasting results of high preoperative LMR associated with POCD.[28] Despite some prior work, the ability of preoperative LMR to predict POCD risk remains unclear. Therefore, a large sample study was conducted to investigate the role of LMR in peripheral blood in the occurrence of POCD and its predictive ability after major abdominal surgery and to provide a reference for prevention and intervention in the occurrence of POCD.

Materials and Methods

Study Design and Patients Selection

A single-center, prospective cohort study was performed at the First Affiliated Hospital of Anhui Medical University from January 2019 to January 2022. This study was approved by the Clinical Medical Research Ethics Committee of the First Affiliated Hospital of Anhui Medical University (20180232) and registered in the Chinese Clinical Trial Registry (ChiCTR1800017632). This study complies with the Declaration of Helsinki. Written informed consent was obtained from each participant.

A flowchart of the patient selection is shown in Figure 1. Inclusion criteria were as follows: (1) age > 40 years; (2) elective major abdominal surgery (defined as operations creating any gastrointestinal anastomosis or involving parenchymal resection of the liver or pancreas[29]) in our hospital; and (3) American Society of Anesthesiologists (ASA) grades I–III. Exclusion criteria were as follows: (1) baseline Mini-Mental State Examination (MMSE) scores below 24; (2) central nervous system disease; (3) psychiatric and psychological diseases, such as anxiety and depression; (4) drug dependence and substance abuse in the past three months; (5) inability to visit and communicate; (6) refusal to participate in. Elimination criteria were as follows: (1) surgeries cancelled; (2) postoperative ICU admission; (3) patients with secondary surgery; (4) patients with serious adverse events such as excessive bleeding during surgery or cardiac arrest; (5) postoperative hospital stay of less than 7 days; and (6) incomplete data records.

Anesthesia Management

Standard monitoring, including pulse oxygen saturation, electrocardiogram, heart rate, end-tidal CO_2 pressure ($P_{ET}CO_2$), and non-invasive blood pressure, was initiated on arrival in the operating room. Ultrasound-guided radial artery puncture was performed under local anesthesia. Midazolam 0.02–0.05 mg/kg, sufentanil 0.2–0.3 ug/kg, etomidate 0.2–0.3 mg/kg, and cis-atracurium 0.2–0.3 mg/kg were injected intravenously for anesthesia induction. Temperature sensors were inserted into the nasal cavity to monitor the body temperature. The BIS was maintained between 45 to 55 by target-controlled infusion of propofol (1.0–4.0μg/mL), continuous infusion of remifentanil (0.1–1.0μg/kg/min) and cis-atracurium (1.0–2.0μg/kg/min). Mechanical ventilation was performed with small tidal volume protective ventilation to maintain the $PETCO_2$ at 35–45 mmHg. During the perioperative period, vasoactive drugs were administered to maintain hemodynamic stability.

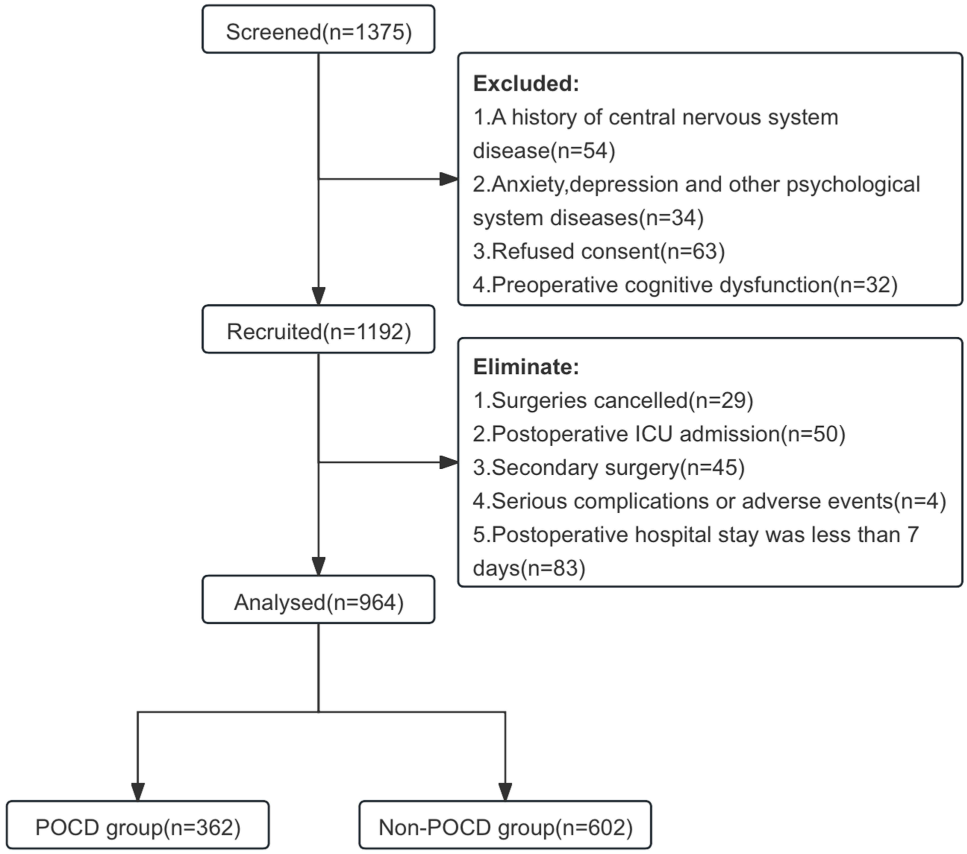

Figure 1 The flow chart of the study design.

Data Collection

On admission, we collected data on demographic factors, including sex, age, body mass index (BMI) and education. The patients' disease history and possible confounding factors during the perioperative period (operation time, anesthesia time and hospital stays) were recorded. Serum biochemical parameters and white blood cell counts were examined and recorded on the day before surgery. Blood was collected at around 6 a. m. Hematology analyzers were used to conduct a complete blood count by department of clinical laboratory, and the results were collected thought electronic medical record system.

Cognitive Function Measurement

A series of neuropsychological tests for both patients and 117 control subjects was performed the day before and 7 days after surgery (or at matched time points for control subjects). 117 control subjects were enrolled according to the above inclusion and exclusion criteria and did not receive surgical anesthesia. Neuropsychological tests were performed in a quiet room with only the subjects and the evaluator present. These tests included the Mini-Mental State Examination (MMSE), verbal fluency test (VFT), digit span test (DST), color trail test (CTT), and Stroop color and word test (SCWT).

Delayed neurocognitive recovery was diagnosed using the International Study of Post-Operative Cognitive Dysfunction 1 definition.[6] To exclude potential bias from the practice effects in cognitive testing, the average practice effect ($\Delta X_{control}$) and standard deviation ($SD[\Delta X_{control}]$) for each neuropsychological test were determined by comparing the test scores at baseline of control subjects at baseline with those 7 days later. For each patient, the *Z* score for each test was calculated by determining the difference between the postoperative and preoperative scores (ΔX), subtracting $\Delta X_{control}$ from ΔX, and then dividing by SD ($\Delta X_{control}$). The sign was adjusted so that negative *Z* scores indicated deterioration from the baseline test. The combined *Z* score ($Z_{combined}$) was calculated by using the sum of *Z* scores for all test (ΣZ) divided by the standard deviations for this sum of *Z* scores in control subjects ($SD[\sum Z_{control}]$). For the DST test, we calculated the Z scores for repeating numbers in the same and opposite order, which corresponded to two tests. For both CTT and SCWT, we recorded both the time and the number of errors and calculated different Z scores. POCD was diagnosed when two or more Z scores were less than −1.96 or the combined Z score was less than −1.96.

$$Z = \frac{\Delta \text{X} - \Delta \text{Xcontrol}}{\text{SD}(\Delta \text{Xcontrol})}$$

$$Z\text{combined} = \frac{\Sigma \text{Z}}{\text{SD}(\Sigma \text{Zcontrol})}$$

Statistical Analysis

Sample size calculation was performed using PASS software, with 80% power, 0.05 alpha. Referring to previous studies, the incidence of POCD one week after surgery in patients (over 40 years old) was 35.6%.[5] And when low LMR can reduced the incidence of POCD one week after surgery by 30% (ie to 24.9%) and considering a 20% dropout rate, a minimum of 358 patients were required in each group.

Analysis was performed using the SPSS software, version 25.0 (IBM SPSS). Continuous variables were presented as mean with standard deviation (SD) or median with interquartile range (IQR), compared by Student's *t*-test or Mann–Whitney *U*-test. Categorical variables were presented as numbers (percentages), and differences between groups were tested by chi-square test or Fisher's exact test. Univariate Logistics regression analysis was used to study the variables related to the occurrence of POCD. Multivariate logistic regression analysis was used to investigate the effect of LMR on the occurrence of POCD after controlling for confounding factors. The data were classified according to the quartiles of LMR, and then the relationship between the occurrence of POCD and the changing trend of LMR was analyzed by multivariate logistic regression analysis. The receiver operating characteristic (ROC) approach was used to determine the optimal threshold for predicting POCD with LMR values, while the area under the curve (AUC), 95% confidence interval (CI) and the cutoff value were reported. In addition, interaction and subgroup analyses were performed according to age, sex, type of surgery, and hypertension using logistic regression models. P<0.05 was considered statistically significant.

Results

Study Population

A total of 1375 cases were screened. After exclusion and elimination, the final 964 patients were included in the analysis, including 602 patients in the Non-POCD group and 362(37.6%) patients in the POCD group (Figure 1). The neuropsychological tests for the 964 patients and 117 control subjects are shown in Supplementary Tables 1 and 2.

Table 1 summarizes the clinical and laboratory characteristic of the patients. The median age of POCD group was significantly higher than that of the Non-POCD group (P = 0.003). Compared with the patients in the Non-POCD group, more patients had hypertension (P = 0.026) and more patients underwent open surgery (P < 0.001). Preoperative monocyte (P < 0.001) was lower in the POCD group compared to that in the Non-POCD group. Preoperative lymphocyte (P < 0.001), LMR (P < 0.001), and hospital stays (P = 0.002) were higher in the POCD group compared to that in the Non-POCD group.

Association Between LMR and POCD Occurrence

To explore the relationship between LMR and POCD, we performed a univariate logistic regression analysis. As shown in Table 2, age (P = 0.004), type of surgery (P<0.001), hypertension (P = 0.027), preoperative lymphocyte (P < 0.001), preoperative monocyte (P<0.001) and LMR (P<0.001) were significantly correlated with POCD in patients after abdominal operation. Multivariate logistic regression analysis was performed to control for other potential confounding variables (Table 3). Model 1 is unadjusted and elevated LMR levels were significantly associated with reduced risk of POCD (odds ratio [OR] = 0.560, 95% CI: 0.507–0.618, P < 0.001). In Model 2, age and sex were adjusted and the association between LMR and POCD remained significant (OR = 0.561, 95% CI: 0.508–0.620, P < 0.001). Based on model 2, we additionally adjusted for type of surgery, hypertension, preoperative lymphocyte and monocyte in model 3,

Table 1 Clinical and Laboratory Characteristic of Study Population

Variables	Non-POCD Group (n=602)	POCD Group (n=362)	P-value
Age(years)	60.0 (54.0–67.0)	63.0 (55.0–70.0)	0.003
Sex			0.389
Female	182 (30.2)	100 (27.6)	
Male	420 (69.8)	262 (72.4)	
BMI (kg/m^2)	22.5 (20.6–24.5)	22.2 (20.6–24.1)	0.167
Education level(years)	6.0 (3.0–9.0)	6.0 (3.0–9.0)	0.121
ASA			0.272
I	10 (1.7)	5 (1.4)	
II	351 (58.3)	193 (53.3)	
III	241 (40.0)	164 (45.3)	
Surgical site			0.150
Stomach and intestines	539 (89.5)	313 (85.5)	
Liver and gall	63 (10.5)	49 (13.5)	
Type of surgery			<0.001
Open	302 (50.2)	233 (64.4)	
Laparoscope	300 (49.8)	129 (35.6)	
Medical history			
Hypertension	178 (29.6)	132 (36.5)	0.026
Diabetes	62 (10.3)	40 (11.0)	0.714
CVD	13 (2.2)	12 (3.3)	0.274
MMSE	27.0 (26.0–28.0)	27.0 (26.0–28.0)	0.436
Preoperative creatinine(μmol/L)	70.0 (61.0–82.0)	70.0 (62.0–82.0)	0.696
Preoperative hemoglobin(g/L)	130.0 (112.0–143.0)	127.5 (111.0–141.0)	0.167
Preoperative lymphocyte(×10^9/L)	1.6 (1.2–2.0)	1.4 (1.0–1.6)	<0.001
Preoperative monocyte(×10^9/L)	0.3 (0.3–0.5)	0. 4 (0.3–0.6)	<0.001
LMR	4.5 (3.4–5.7)	3.0 (2.0–4.0)	<0.001
Duration of operation(min)	170.0 (125.0–235.0)	180.0 (127.0–235.0)	0.621
Duration of anesthesia(min)	190.0 (140.5–255.0)	200.0 (145.0–260.0)	0.615
Hospital stays(days)	15.0 (13.0–19.0)	16.0 (13.0–19.5)	0.002

Notes: Data are presented as median (interquartile range) or n (%).
Abbreviations: POCD, postoperative cognitive dysfunction; BMI, body mass index; ASA, American Society of Anesthesiologists; CVD, coronary artery disease; MMSE, Mini-mental state examination; LMR, lymphocyte-to-monocyte ratio.

and the association between LMR and POCD still remained significant (OR = 0.628, 95% CI: 0.502–0.785, P < 0.001). To further explore the linkage between LMR and POCD, we divided LMR into four levels based on quartiles. Compared with the lowest level (Q1), the highest level of LMR(Q4) was significantly associated with a decreased risk of developing POCD (OR = 0.292, 95% CI: 0.123–0.695, P = 0.005) (P for trend = 0.003, Table 4).

According to the ROC curve, a cutoff value of 3.758 (specificity: 66.5%, sensitivity: 71.8%) of the preoperative LMR level could be used to predict POCD occurrence and AUC was 0.747 (95% CI: 0.715–0.779, P < 0.001, Figure 2). POCD was observed in 56.3% of the patients in the low LMR group (LMR < 3.758) and only 20.3% of the patients in the high LMR group (Figure 3).

Subgroup Analyses

To determine the influence of important variables on the relationship between the LMR and POCD, we performed a series of subgroup analyses. The results of subgroup analyses are shown in Figure 4. The results of the subgroup analyses were consistent with the primary ones, and no heterogeneity was observed in the subgroup analyses (P for interaction > 0.05).

Table 2 Univariate Logistic Regression Analysis of Risk Factors for Postoperative Cognitive Dysfunction

Variables	Univariate Logistic Regression		
	OR	**95% CI**	**P-value**
Age(years)	1.021	1.006–1.036	0.004
Female	0.881	0.660–1.176	0.389
BMI (kg/m^2)	0.969	0.927–1.012	0.154
Education level(years)	0.977	0.946–1.009	0.155
ASA>II	1.241	0.953–1.615	0.109
Liver and gall surgery	1.339	0.899–1.995	0.151
Open surgery	1.794	1.373–2.346	<0.001
Hypertension	1.367	1.037–1.802	0.027
Diabetes	1.082	0.710–1.648	0.714
CVD	1.553	0.701–3.442	0.278
MMSE	0.967	0.890–1.051	0.431
Preoperative creatinine(μmol/L)	0.997	0.991–1.004	0.461
Preoperative hemoglobin(g/L)	0.997	0.992–1.003	0.313
Preoperative lymphocyte(×10^9/L)	0.359	0.273–0.473	<0.001
Preoperative monocyte(×10^9/L)	21.182	9.376–47.855	<0.001
LMR	0.560	0.507–0.618	<0.001
Duration of operation(min)	1.000	0.999–1.002	0.630
Duration of anesthesia(min)	1.001	0.999–1.002	0.525

Abbreviations: POCD, postoperative cognitive dysfunction; BMI, body mass index; ASA, American Society of Anesthesiologists; CVD, coronary artery disease; MMSE, Mini-mental state examination; LMR, lymphocyte-to-monocyte ratio.

Table 3 Risk for Postoperative Cognitive Dysfunction According to Lymphocyte-to-Monocyte Ratio

Variables	Multivariate Logistic Regression		
	OR	**95% CI**	**P-value**
Model 1	0.560	0.507–0.618	<0.001
Model 2	0.561	0.508–0.620	<0.001
Model 3	0.628	0.502–0.785	<0.001

Notes: Model 1 is univariate analysis. Model 2 is adjusted by age, sex. Model 3 is adjusted by age, type of surgery, hypertension, preoperative lymphocyte and monocyte.
Abbreviations: OR, odds ratio; CI, confidence interval.

Table 4 Association Analysis of Lymphocyte-to-Monocyte Ratio in Quartiles with POCD

Variables	No. of Patients (n, %)		Logistic Regression	
	Non-POCD Group	**POCD Group**	**OR (95% CI)**	**P-value**
LMR				
Q1(<2.78)	79 (13.1)	162 (44.8)	Reference level	1
Q2(2.78–3.86)	137 (22.8)	103 (28.5)	0.603(0.366–0.993)	0.047
Q3(3.86–5.34)	184 (30.6)	58 (16.0)	0.351(0.181–0.682)	0.002
Q4(≥5.34)	202 (33.6)	39 (10.8)	0.292(0.123–0.695)	0.005
P for trend				0.003

Notes: P-value is calculated using a multivariate logistic regression adjusted by age, type of surgery, hypertension, preoperative lymphocyte and monocyte.
Abbreviations: OR, odds ratio; CI, confidence interval; POCD, postoperative cognitive dysfunction; LMR, lymphocyte-to-monocyte ratio.

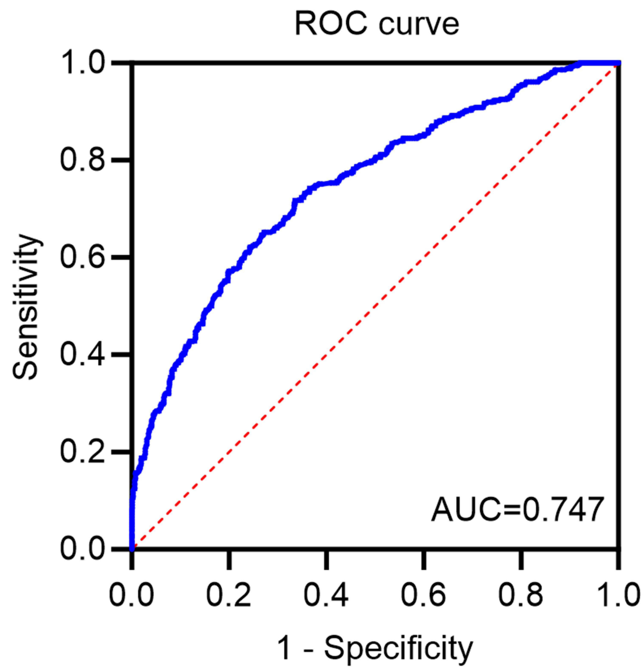

Figure 2 Receiver operating characteristic curve for lymphocyte-to-monocyte ratio as a predictor of postoperative cognitive dysfunction.

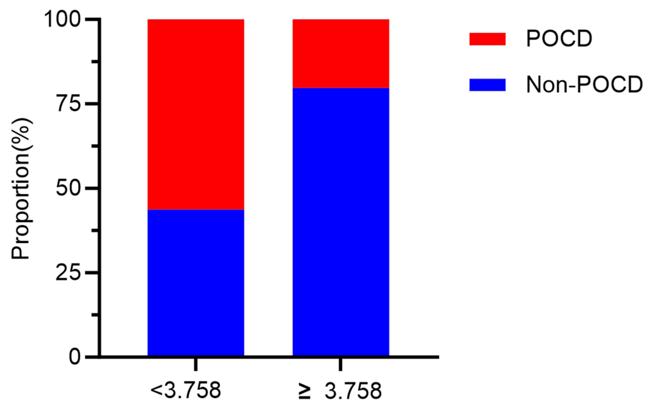

Figure 3 Comparison of the incidence of postoperative cognitive dysfunction of different lymphocyte-to-monocyte ratio levels.

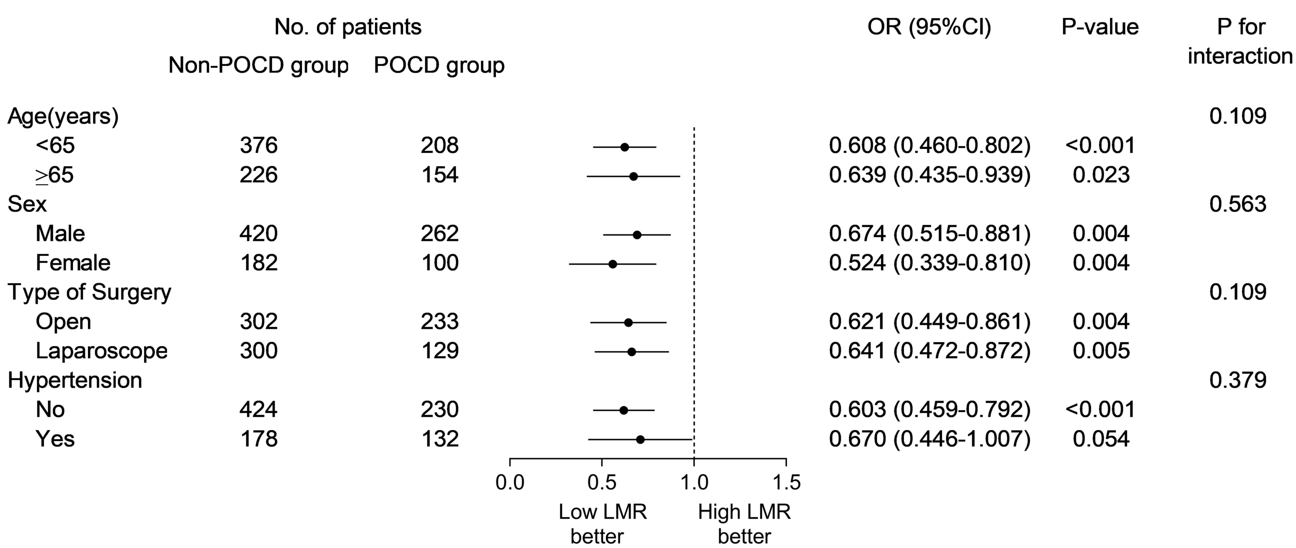

Figure 4 Subgroup analyses of association between lymphocyte-to-monocyte ratio and postoperative cognitive dysfunction in patients with major abdominal surgery.

Discussion

In this study, we found that a preoperative low LMR were significantly associated with the development of POCD in an analysis of 964 patients undergoing major abdominal surgery. The association remains when accounting for the common risks, such as age, sex, type of surgery, perioperative factors etc. Moreover, LMR was an independent risk factor for predicting POCD occurrence.

POCD is one of the most common postoperative complications in patients and its diagnosis relies on rating scales. However, the rating scales are not widely used because of their time-consuming and laborious process.[30] Therefore, it is important to determine the relationship between some routine preoperative examinations and POCD. Monocytes are important markers of innate immunity, whereas lymphocytes are the primary effector cells of the adaptive immune response.[31–33] Dysfunctional immunity may lead to increased chronic systemic inflammation.[34] Previous study has shown that a decrease in lymphocytes indicates that the patient is in a state of systemic inflammation, and cognitive decline may occur as a result of an increase in inflammatory responses increasing.[35] Elevated monocytes are also associated with the inflammatory response. Patients with nervous system diseases such as Alzheimer's disease, cerebral trauma and autoimmune encephalitis have elevated monocyte and proinflammatory responses.[36–38] In our study, we found that patients with POCD had lower preoperative lymphocytes and higher monocytes than those who did not develop POCD. These results indicate that POCD is associated with a systemic inflammatory response. At present, the relationship between inflammation and the pathogenesis of POCD has long been discussed. Proinflammatory cytokines including IL-6, IL-1 and TNF-α have been reported to play a key role in mediating surgery-induced neuroinflammation and cognitive decline after surgery.[9,39,40] Terrando et al verified that surgical trauma engages the innate immune system through NF-κB–dependent signaling to release cytokines that disrupt BBB integrity. Through the permeable BBB, peripheral macrophages migrate into the hippocampus, promoting neuroinflammation and impairing cognitive function.[41] Therefore, patients with a low LMR are more likely to have BBB disruption and cognitive decline after anesthesia surgery. In this study, the incidence of POCD in patients with low LMR was as high as 56.3%, while the incidence of POCD in patients with high LMR was 20.3%.

LMR is a combination of lymphocytes and monocytes and has been reported to be a potential novel biomarker of the inflammatory response.[42] Low LMR levels have been used as a biomarker to predict the outcomes of many diseases.[24,26,43,44] Lu et al demonstrated that the preoperative NLR, LMR and SII were related to postoperative cognitive decline.[27] Our results are similar to these findings. A preoperative low LMR can predict the occurrence of POCD after major abdominal surgery. However, in a study on cardiovascular surgery, a preoperative high LMR level was associated with poor postoperative neurocognitive function.[28] The differences may be due to the sample size and POCD assessment methods. Our study had a large sample size, which reduced the risk of confounding factors and bias. We performed a series of neuropsychological tests and used the Z-score method to diagnose POCD. In this study, the incidence of POCD after major abdominal surgery was 37.6%, which is similar to that reported in previous studies.[5] The International Study of Postoperative Cognitive Dysfunction 1 reported a 25.8% prevalence of POCD at 1 week, whereas McDonagh et al found that the incidence of POCD still exceeded 50% at 6 weeks after surgery.[4,6] This may be because we included patients who underwent abdominal surgery or may be attributable to differences in methodology, including the definition and diagnosis of POCD. Despite the differing rates of POCD, advancing age was considered as a risk factor for POCD in all three studies and our study. However, in the subgroup analysis, the role of LMR to predict occurrence of POCD in patients of different ages undergoing abdominal surgery has no difference.

Despite the advances in research on POCD, patients who have already developed POCD have no effective treatment. Therefore, it is important to warn about the potential risk of POCD using preoperative biomarkers, such as low LMR. In addition, a high preoperative LMR could allow the surgeon, anesthesiologists, and nurses to reduce the occurrence of POCD. For example, preoperative cognitive training, careful selection of anesthetics, closer monitoring of intraoperative anesthesia depth and rational fluid therapy can reduce the occurrence of POCD.[45–48] Moreover, dietary modifications (supplementation with vitamins and Omega-3) can improve immune function, and cognitive function.[49,50]

This study had some limitations. Firstly, we only recorded the preoperative LMR, and we did not record postoperative LMR and inflammatory factors, such as plasma IL-6 and TNF-α. We aimed to explore the relationship between preoperative inflammatory markers and POCD, to prevent the occurrence of POCD. Secondly, we lacked long-term follow-up data of patients, such as cognitive assessment at 1 month or even 1 year after surgery. Thirdly, we only included patients who underwent major abdominal surgery, and other types of surgery require further studies. Fourthly, We did not record the postoperative medication use of patients, and different medications may have an impact on the occurrence of POCD in patients, such as anti-inflammatories, anti-microbials, and analgesics.

Conclusion

In summary, our study showed that preoperative low LMR is associated with the development of POCD after major abdominal surgery. Preoperative LMR level in the peripheral blood is an effective predictor of POCD after major abdominal surgery. Surgery, anesthesia and postoperative care should be performed more cautiously in patients with extremely abnormal inflammatory markers. More prospective multicenter studies are needed to validate our findings and animal study are needed to elucidate the underlying mechanisms between inflammatory markers and POCD.

Data Sharing Statement

The data used to support the findings of this study are available from the corresponding author upon request.

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An unauthorized version of the Chinese MMSE was used by the study team without permission, however this has now been rectified with PAR. The MMSE is a copyrighted instrument and may not be used or reproduced in whole or in part, in any form or language, or by any means without written permission of PAR (www.parinc.com).

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Disclosure

The authors report no conflicts of interest in this work.

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