

Neutrophil-lymphocyte Ratio as a Predictor of Delirium in Older Hospitalized Patients: A Prospective Cohort Study

Yanli Zhao

Sichuan University West China Hospital

Jirong Yue (✉ yuejirong11@hotmail.com)

Sichuan University West China Hospital

Taiping Lin

west china hospital

Xuchao Peng

Sichuan University West China Hospital

Dongmei Xie

Sichuan University West China Hospital

Langli Gao

Sichuan University West China Hospital

Xiaoyu Shu

Sichuan University West China Hospital

Chenkai Wu

Duke Kunshan University

Research

Keywords: Delirium, Older people, Neutrophil-lymphocyte ratio

Posted Date: August 28th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-64372/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Neutrophil-lymphocyte ratio as a predictor of delirium in older hospitalized patients: a prospective cohort study

Yanli Zhao ¹, Jirong Yue ^{1,*}, Taiping Lin ¹, Xuchao Peng ¹, Dongmei Xie ¹, Langli Gao ¹, Xiaoyu Shu ¹, and Chenkai Wu²

¹ Department of Geriatrics and National Clinical Research Center for Geriatrics, West China Hospital of Sichuan University, Chengdu 610041, Sichuan, China.

² Global Health Research Center, Duke Kunshan University, Kunshan, Jiangsu, China

*Corresponding author: email: yuejirong11@hotmail.com; Phone: +086 18980601143

Abstract

Background: Delirium is a common neuropsychiatric syndrome in older hospitalized patients. Previous studies have suggested that inflammation and oxidative stress contribute to the pathophysiology of delirium. However, it remains unclear whether neutrophil-lymphocyte ratio (NLR), an indicator of systematic inflammation, is associated with delirium. This study aimed to investigate the value of NLR as a predictor of delirium among older hospitalized patients.

Methods: We conducted a prospective study of 740 hospitalized patients aged ≥ 70 years at the West China Hospital of Sichuan University. Neutrophil and lymphocyte counts were collected within 24 hours after hospital admission. Delirium was assessed on admission and every 48 hours thereafter. We used the Receiver operating characteristic analysis to assess the ability of the NLR for predicting delirium. The optimal cut-point value of the NLR was determined based on the highest Youden index (sensitivity + specificity - 1). Patients were categorized according to the cut-point value and quartiles of NLR, respectively. We then used logistic regression to identify the unadjusted and adjusted associations between NLR as a categorical variable and delirium.

Results: The optimal cut-point value of NLR for predicting delirium was 3.626 (sensitivity: 75.2%; specificity: 63.4%; Youden index: 0.386). The incidence of delirium was significantly higher in patients with $NLR > 3.626$ than $NLR \leq 3.626$ (24.5% vs 5.8%; $P < 0.001$). Significantly fewer patients in the first quartile of NLR experienced delirium than in the 3rd (4.3% vs 20.0%; $P < 0.001$) and 4th quartiles of NLR (4.3% vs 24.9%; $P < 0.001$). Multivariable logistic regression analysis showed that NLR was independently associated with delirium.

Conclusions: NLR is a simple and practical marker that can predict the development of delirium in older hospitalized patients.

Keywords: Delirium, Older people, Neutrophil-lymphocyte ratio

Background

Delirium is an acute neuropsychiatric syndrome characterized by disturbances in consciousness, cognition and attention [1]. Delirium is a common complication among hospitalized older patients and associated with a variety of adverse outcomes, including cognitive impairment, prolonged hospital stay, functional disability, and, mortality [2-5].

Diagnosis of delirium is primarily based on clinical observation and its underlying pathophysiology is not entirely understood [6]. Inflammation and oxidative stress have been reported to play a key role in the development of delirium [7, 8]. Systemic inflammation could lead to neuro-inflammation and resultant delirium through activation of brain parenchymal cells and an expression of cytokines in the brain [9]. Recent studies have demonstrated associations between traditional inflammatory markers and delirium, such as C-reactive protein (CRP), interleukin (IL)-6, IL-8, IL-2, and tumor necrosis factor (TNF) [10-14]. However, the clinical utility of these biomarkers has been limited due to relatively high costs and inconvenience to measure. Hence, identification of simple inflammatory markers, easily available in every health care setting, is essential to improve delirium recognition and prediction among older patients.

The neutrophil-lymphocyte ratio (NLR), obtained easily from the circulation, is an indicator of inflammation and oxidative stress [15]. NLR has been applied to prognosis evaluation in various disciplines including malignancies, cardiovascular diseases, kidney diseases, and sepsis [16-20]. Additionally, several studies have reported a relationship between increased NLR and neurological or psychiatric conditions, such as Alzheimer's disease, schizophrenia, Parkinson's disease, ischemic stroke as well as memory disorders [15, 21, 22]. However, studies investigating the effect of NLR on delirium in older hospitalized patients are rare.

The present study aimed to explore the relationship between NLR and delirium among hospitalized older patients. We hypothesized that older hospitalized patients with an elevated level of NLR would be more likely to experience delirium.

Methods

Study population

We conducted a prospective cohort study at the Department of Geriatric, West China hospital of Sichuan from March of 2016 to July of 2017. Included patients were ≥ 70 years and had an anticipated length of stay of more than 2 days. Exclusion criteria were the presence of delirium on admission, severe hearing impairment, inability to communicate due to severe dementia or psychiatric illness, a terminal condition with life expectancy < 6 months, and incomplete data. The study was performed in accordance with the Declaration of Helsinki and approved by the Institutional Review Boards of West China Hospital, Sichuan University. Written informed consent was obtained from all participants.

Data collection

All patients were assessed by trained research nurses within 24 h of admission. Demographic and general clinical characteristics including age, gender, living situation, education level, marriage status, smoking, alcohol intake, and type of admission were recorded. Peripheral blood samples were collected from patients to measure neutrophil and lymphocyte counts. The NLR was calculated by dividing the neutrophil count by the lymphocyte count. Severity of comorbidities was evaluated using the Charlson Comorbidity Index (CCI), a score based on 19 chronic diseases [23]. Patients were divided into mild (CCI 1-2), moderate (CCI 3-4) and severe (CCI ≥ 5) groups. Cognitive level was assessed using the Short Portable Mental Status Questionnaire (SPMSQ) [24]. Baseline functional status was measured by the Barthel Index for activities of living (ADL) [25]. Visual acuity and hearing ability were assessed with the Snellen eye chart and the whispered voice test, respectively.

Delirium screening

Patients were screened for delirium by trained research assessors within 24 h of admission and every 48 h thereafter until discharge or for a maximum of 13 days. Delirium was assessed using the Confusion Assessment Method (CAM) based on the

criteria of the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* (DSM-IV) [26, 27]. The CAM is a widely used diagnostic tool for delirium with a sensitivity of 94%, a specificity of 89%, and a Kappa's inter-rater reliability between 0.70 and 1.00 [28]. The CAM is based on the following four features: (i) acute onset and fluctuating course; (ii) inattention; (iii) disorganized thinking; and (iv) altered level of consciousness. Patients were considered delirious if they displayed features (i) and (ii), with either (iii) or (iv).

Statistical analysis

Descriptive data were expressed as number and percentage for categorical variables and as medians with the interquartile range (IQR) for continuous variables. Comparison between categorical variables was done using the chi-square test. Continuous variables were compared with the Mann-Whitney U-test or Kruskal-Wallis test. Receiver operating characteristic (ROC) curve analysis was performed and Youden index was calculated as "sensitivity + specificity - 1". NLR that yielded the highest Youden index was determined as the optimal cut-point value for predicting delirium. Participants were grouped based on NLR quartiles and the optimal cut-point value of NLR. We then used logistic regression models to examine the unadjusted and adjusted associations between NLR as a categorical variable and delirium. The multivariate logistic regression model was adjusted for age, sex, alcohol use, smoking, vision impairment, hearing impairment, cognitive impairment, disability, and CCI.

All statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY). P -value ≤ 0.05 was considered significant.

Results

Of 740 patients included in the analysis, the median age was 84 years (IQR: 79-87 years) and the majority was male (71.2%). The median NLR value and length of hospital stay were 3.1 (IQR: 2.1-5.7) and 17 days (IQR: 12-26 days), respectively. During hospital stay, 101 patients (13.6%) were diagnosed with delirium. Other baseline characteristics of all patients are presented in Table 1.

An ROC curve was performed to identify the predictive ability of NLR for delirium. The area under the ROC curve (AUC) of NLR was 0.714 (95% CI 0.66-0.77; $P < 0.001$). The optimal cut-point value of NLR for predicting delirium was 3.636 determined by the highest Youden index (sensitivity, 75.2%; specificity, 63.4%) (Figure 1).

Participants' characteristics by the cut-point value of NLR are shown in Table 1. Compared to patients with NLR value ≤ 3.626 , those with NLR value > 3.626 tended to be older, formally educated, smoking, impaired hearing, impaired vision. Patients with NLR value > 3.626 had a higher emergency admission rate, higher rates of cognitive impairment, lower Barthel Index and higher CCI. In particular, significantly more patients with NLR > 3.626 were diagnosed with delirium than those with NLR ≤ 3.626 .

Table 1 Patient characteristics by neutrophil-lymphocyte ratio (NLR) ≤ 3.626 and > 3.626

Characteristic	Total (n=740)	NLR ≤ 3.626 (n=430)	NLR > 3.626 (n=310)	P-value ^a
Age (years), median (IQR)	84 (79-87)	83 (77-86)	85 (81-88)	<0.001
Male gender, n (%)	527 (71.2)	297 (69.1)	230 (74.2)	0.129
Living alone, n (%)	31 (4.2)	17 (4.0)	14 (4.5)	0.706
Married, n (%)	610 (82.4)	364 (84.7)	246 (79.4)	0.062
Education, n (%)				
Illiteracy or primary school	111 (15.0)	58 (13.5)	53 (17.1)	
Middle school	133 (18.0)	69 (16.0)	64 (20.6)	0.022
High school or above	496 (67.0)	303 (70.5)	193 (62.3)	
Alcohol abuse, n (%)	149 (20.1)	84 (19.5)	65 (21.0)	0.632
Smoker, n (%)	283 (38.2)	150 (34.9)	133 (42.9)	0.027
Vision impairment, n (%)	243 (32.8)	136 (31.6)	107 (34.5)	0.409
Hearing impairment, n (%)	229 (30.9)	127 (29.5)	102 (32.9)	0.328
Cognitive impairment, n (%)	243 (31.6)	89 (20.7)	145 (46.8)	<0.001
Emergency admission, n (%)	97 (13.1)	25 (5.8)	72 (23.2)	<0.001
Barthel index, median (IQR)	80 (55-95)	90 (70-100)	65 (40-85)	<0.001
CCI, n (%)				
Mild (≤ 2)	566 (76.5)	344 (80.0)	222 (71.6)	
Moderate (3-4)	136 (18.4)	72 (16.7)	64 (20.6)	0.005
Severe (≥ 5)	38 (5.1)	14 (3.3)	24 (7.7)	
NLR, median (IQR)	3.1 (2.1-5.7)	2.2 (1.7-2.8)	6.6 (4.8-9.4)	<0.001
Delirium, n (%)	101 (13.6)	25 (5.8)	76 (24.5)	<0.001

NLR neutrophil-lymphocyte ratio, CCI Charlson Comorbidity Index, IQR interquartile range.

Notes: ^a P values according to Mann-Whitney U or Chi-square tests

Participants' characteristics by NLR quartiles are shown in Table 2. There were significantly differences in age, education, smoking, cognitive impairment, emergency admission, the Barthel Index and comorbidities among different NLR categories. Compared to those in the first quartile of NLR, patients in the 3rd and 4th quartiles of NLR had a greater proportion of delirium.

Table 2 Patient characteristics by quartile categorization

Characteristic	NLR Quartiles				P-value ^a
	<2.055 (n=185)	2.055-3.110 (n=185)	3.111-5.735 (n=185)	>5.735 (n=185)	
Age (years), median (IQR)	83 (79-86)	83 (76-86)	85 (80-88)	85 (81-88)	<0.001
Male gender, n (%)	126 (68.1)	125 (67.6)	144 (77.8)	132 (71.4)	0.110
Living alone, n (%)	8 (4.3)	6 (3.2)	10 (5.4)	7 (3.8)	0.758
Married, n (%)	160 (86.5)	155 (83.8)	153 (82.7)	142 (76.8)	0.091
Education, n (%)					
Illiteracy or primary school	17 (9.2)	31 (16.8)	27 (14.6)	36 (19.5)	
Middle school	24 (13.0)	31 (16.8)	39 (21.1)	39 (21.1)	0.002
High school or above	144 (77.8)	123 (66.5)	119 (64.3)	110 (59.5)	
Alcohol abuse, n (%)	149 (20.1)	84 (19.5)	65(21.0)	33 (17.8)	0.285
Smoker, n (%)	57 (30.8)	71 (38.4)	72 (38.9)	83 (44.9)	0.050
Vision impairment, n (%)	61 (33.0)	57 (30.8)	66 (35.7)	59 (31.9)	0.778
Hearing impairment, n (%)	53 (28.6)	58 (31.4)	58 (31.4)	60 (32.4)	0.879
Cognitive impairment, n (%)	33 (17.8)	41 (22.2)	68 (36.8)	92 (49.7)	<0.001
Emergency admission, n (%)	5 (2.7)	14 (7.6)	27 (14.6)	51 (27.6)	<0.001
Barthel index, median (IQR)	95 (75-100)	90 (65-100)	80 (47-95)	55 (35-80)	<0.001
CCI, n (%)					
Mild (≤ 2)	152 (82.2)	151 (81.6)	141 (76.2)	122 (65.9)	
Moderate (3-4)	28 (15.1)	28 (15.1)	38 (20.5)	42 (22.7)	<0.001
Severe (≥ 5)	5 (2.7)	6 (3.2)	6 (3.2)	21 (11.4)	
NLR, median (IQR)	1.6 (1.3-1.8)	2.6 (2.3-2.8)	4.0 (3.5-4.9)	8.3 (7.1-12.3)	<0.001
Delirium, n (%)	8 (4.3)	10 (5.4)	37 (20.0)	46 (24.9)	<0.001

NLR neutrophil-lymphocyte ratio, CCI Charlson Comorbidity Index, IQR interquartile range.

Notes: ^a P values according Kruskal-Wallis or Chi-square tests

The univariate logistic regression showed a significant association of delirium with age, smoking, vision impairment, hearing impairment, cognitive impairment, Barthel Index, CCI, and NLR (Table 3). In the multivariate regression model, NLR >3.626 was significantly associated with higher odds of delirium. When modeled as a categories variable based on NLR quartiles, NLR was also found to be independently associated with delirium (Table 4).

Table 3 Univariate logistic regression analysis of potential risk factors for delirium

Variable	Unadjusted OR (95%CI)	P-value
Age	1.14 (1.09-1.19)	<0.001
Male gender	1.05(0.67-1.67)	ns
Alcohol abuse	1.05 (0.62-1.76)	ns
Smoker	1.71 (1.12-2.61)	0.013
Vision impairment	2.61 (1.71-3.99)	<0.001
Hearing impairment	2.08 (1.36-3.20)	0.001
Cognitive impairment	56.95 (24.44-132.74)	<0.001
Barthel index	0.94 (0.93-0.95)	<0.001
CCI		
Mild (≤ 2)	Reference	
Moderate (3-4)	2.63 (1.61-4.30)	<0.001
Severe (≥ 5)	6.76 (3.35-13.63)	<0.001
NLR >3.626	5.26 (3.26-8.50)	<0.001
NLR quartiles		
<2.055	Reference	
2.055-3.110	1.26 (0.49-3.28)	0.630
3.111-5.735	5.53 (2.50-12.25)	<0.001
>5.735	7.32 (3.35-16.02)	<0.001

NLR neutrophil-lymphocyte ratio, CCI Charlson Comorbidity Index, *QR* odds ratio, *CI* confidence interval, *ns* non statistically significantly

Table 4 Multivariate logistic regression analysis of potential risk factors for delirium

Variable	Adjusted OR (95%CI) ^a	P-value
NLR >3.626 ^b	2.73 (1.40-5.34)	0.003
NLR quartiles ^c		
<2.055	Reference	
2.055-3.110	0.61 (0.17-2.24)	0.457
3.111-5.735	3.75 (1.21-11.62)	0.022
>5.735	2.18 (0.73-6.53)	0.165

NLR neutrophil-lymphocyte ratio, *QR* odds ratio, *CI* confidence interval

Notes: ^a Adjusted for age, sex, alcohol use, smoking, vision impairment, hearing impairment, cognitive impairment, disability, and CCI;

^b Modeled as categories variable by the cut-point of NLR;

^c Modeled as categories variable by NLR quartiles

Discussion

This is the first prospective study conducted in older hospitalized patients investigating the association between NLR as a marker for systemic inflammation and delirium. We found that the median level of NLR was elevated in elderly patients with delirium. Individuals with high NLR were more likely to experience delirium than those

with low NLR. These results suggest that NLR is an important risk factor for delirium among hospitalized older patients and maintaining a low level of an inflammation level may help prevent delirium.

Previous literature suggested that systemic inflammation and oxidative stress might be involved in the development of delirium [7, 8]. Previous studies have reported that inflammatory markers and cytokines can be detected in serum and cerebrospinal fluid of elderly patients with delirium [11, 29-31]. In addition, there are studies showing that inflammatory condition could negatively affect frontotemporal cognitive abilities such as memory, attention and executive functions [32]. The initial immune response to stressful situations is characterized by systemic changes in leucocyte subtypes such as an increase in neutrophils and a decrease in lymphocytes [33], which can lead to an elevated levels of NLR. In fact, the relationship of leucocyte subtypes with delirium or cognitive decline have been investigated in previous studies. For example, the elevation of neutrophil count in elderly patients has been shown to be associated with delirium in previous studies [34]. There is other study indicating the significant association between increased neutrophils and cognitive impairment [35]. In a cohort study, lower levels of lymphocyte have been found to be an independent predictor of delirium [36]. Likewise, one recent study reported that patients with lower levels of lymphocyte were more likely to suffer from delirium [37].

NLR is emerging as a novel marker of systemic inflammation, which integrates information of neutrophils and lymphocytes. Moreover, NLR is different from traditional inflammatory markers (eg, CRP, PCT, IL-6, IL-8, or TNF). NLR is a simple, inexpensive, and readily available inflammatory marker that can be directly derived from white blood cell (WBC) count on admission. Furthermore, NLR is less likely to be influenced by fluid imbalance than the individual WBC subtypes [38]. Compared with conventional parameters such as CRP, the total WBC counts and the individual WBC subtypes, increased NLR has been identified as a more powerful predictor of adverse outcomes in many disciplines [39-41]. In particular, NLR has been reported to have higher predictive value in delirium than CRP, neutrophils and lymphocytes [42]. Therefore, NLR might be better at reflecting a association between systemic

inflammation and delirium than neutrophil or lymphocyte alone.

Limited studies in recent years have investigated the possible association between NLR and delirium. Egberts et al [42] found that in a cohort of acutely ill elderly patients, a raised NLR was an independent predictor of delirium. Additionally, Kotfits et al [43] stated that an increased NLR is significantly associated with increased risk of delirium in patients with acute ischemic stroke. The results of our study are consistent with these previous findings. Moreover, there are studies evaluating the role of NLR as a risk factor for cognitive impairment. Halazun et al [44] demonstrated a contribution of NLR to cognitive dysfunction after carotid endarterectomy. The relationship of NLR with cognitive impairment has been suggested by Liu et al and higher NLR was also found in patients with cognitive decline [45]. Our results added further evidence to the relationship of NLR with delirium or cognitive impairment.

The mechanisms of how systemic inflammation and increased NLR result in delirium are still unclear. Inflammation characterized by increased neutrophils and decreased lymphocytes can reduce plaque stability and promote atherosclerosis, which may increase the risk of delirium through microinfarcts. Furthermore, reactive oxygen species released by neutrophils lead to disruption of the blood-brain barrier (BBB) and increase its permeability, cytokines then migrate across the BBB and activate microglia which will produce reactive oxygen species, the accumulation of cytokines and reactive oxygen species in brain may lead to the process of oxidization and inflammation and eventually result in neurodegeneration [7, 46].

This study was conducted with a large sample of older hospitalized patients, which may reduce selection bias. However, our study had several limitations. First, this was a single-center study that might be insufficient to represent a general population of elderly patients with delirium. Second, a single measurement of NLR on admission does not allow for evaluating the stability of this marker over time and assessing the long-term effect of this marker on delirium. Third, other inflammatory markers (eg, CRP, IL-6, or IL-8), which may have influence on delirium, were not included in our study.

Conclusion

In this study, we found that elevated NLR was significantly associated with increased odds of delirium in older hospitalized patients. The results suggest that NLR can serve as a convenient, inexpensive, and rapidly accessible marker to predict delirium. The findings of this study also underline that systemic inflammation and oxidative stress play a key role in the pathophysiology of delirium. Thus, use of this marker in routine clinical research can help clinicians identify patients who are at risk of delirium, and may help to prevent negative outcomes.

Abbreviations

NLR, neutrophil-lymphocyte ratio; SPMSQ, Short Portable Mental Status Questionnaire; CCI, Charlson Comorbidity Index; CAM, Confusion Assessment Method; CRP, C-reactive protein; TNF, tumor necrosis factor.

Acknowledgments

We would like to thank the staff of the Department of Geriatrics Medicine, West China Hospital and all participants for their great contribution.

Funding

This study was supported by Health Research of Cadres in Sichuan province (SCR 2019-102), Sichuan Science and Technology Program (2019YJ0033).

Availability of data and materials

The datasets used for the current study are available from the corresponding author upon reasonable request.

Author's contributions

JY conceptualized and designed the study. YZ, XP and TL collected and interpreted the data. YZ, DX, LG, XS and CW analyzed data, prepared and reviewed figures. YZ, JY and CW wrote the original draft; all authors reviewed the manuscript.

Ethics approval and consent to participate

Ethics approval was obtained from the Institutional Review Boards of West China

Hospital, Sichuan University. All the participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

¹ Department of Geriatrics and National Clinical Research Center for Geriatrics, West China Hospital of Sichuan University, Chengdu, Sichuan, China. ² Global Health Research Center, Duke Kunshan University, Kunshan, Jiangsu, China.

References

1. Association AP. Diagnostic and Statistical Manual of Mental Disorders (DSM-5). 5th ed. Washington, DC: American Psychiatric Publishing; 2013.
2. Siddiqi N, House AO, Holmes JD. Occurrence and outcome of delirium in medical in-patients: a systematic literature review. *Age Ageing*. 2006;35:350-64.
3. Witlox J, Eurelings LS, de Jonghe JF, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *Jama*. 2010;304:443-51.
4. Eide LS, Ranhoff AH, Fridlund B, Haaverstad R, Hufthammer KO, Kuiper KK, Nordrehaug JE, Norekval TM. Delirium as a Predictor of Physical and Cognitive Function in Individuals Aged 80 and Older After Transcatheter Aortic Valve Implantation or Surgical Aortic Valve Replacement. *J Am Geriatr Soc*. 2016;64:1178-86.
5. Raats JW, van Eijdsden WA, Crolla RM, Steyerberg EW, van der Laan L. Risk Factors and Outcomes for Postoperative Delirium after Major Surgery in Elderly Patients. *PLoS One*. 2015;10:e0136071.
6. Inouye SK, Westendorp RG, Saczynski JS. Delirium in elderly people. *Lancet*. 2014;383:911-22.
7. Maldonado JR. Neuropathogenesis of delirium: review of current etiologic theories and common pathways. *Am J Geriatr Psychiatry*. 2013;21:1190-222.
8. Egberts A, Fekkes D, Wijnbeld EH, van der Ploeg MA, van Saase JL, Ziere G, van der Cammen TJ, Mattace-Raso FU. Disturbed Serotonergic Neurotransmission and Oxidative Stress in Elderly Patients with Delirium. *Dement Geriatr Cogn Dis Extra*. 2015;5:450-8.
9. Cerejeira J, Firmino H, Vaz-Serra A, Mukaetova-Ladinska EB. The neuroinflammatory hypothesis of delirium. *Acta Neuropathol*. 2010;119:737-54.
10. Zhang Z, Pan L, Deng H, Ni H, Xu X. Prediction of delirium in critically ill patients with elevated C-reactive protein. *J Crit Care*. 2014;29:88-92.
11. van Munster BC, Korevaar JC, Zwinderman AH, Levi M, Wiersinga WJ, De Rooij SE. Time-course of cytokines during delirium in elderly patients with hip fractures. *Journal of the American Geriatrics Society*. 2008;56:1704-9.
12. Kazmierski J, Banys A, Latek J, Bourke J, Jaszewski R. Raised IL-2 and TNF- α concentrations are

- associated with postoperative delirium in patients undergoing coronary-artery bypass graft surgery. *International psychogeriatrics*. 2014;26:845-55.
13. Dillon ST, Vasunilashorn SM, Ngo L, Otu HH, Inouye SK, Jones RN, Alsop DC, Kuchel GA, Metzger ED, Arnold SE, Marcantonio ER, Libermann TA. Higher C-Reactive Protein Levels Predict Postoperative Delirium in Older Patients Undergoing Major Elective Surgery: A Longitudinal Nested Case-Control Study. *Biol Psychiatry*. 2017;81:145-53.
 14. Ritter C, Tomasi CD, Dal-Pizzol F, Pinto BB, Dyson A, de Miranda AS, Comim CM, Soares M, Teixeira AL, Quevedo J, Singer M. Inflammation biomarkers and delirium in critically ill patients. *Crit Care*. 2014;18:R106.
 15. Kulaksizoglu B, Kulaksizoglu S. Relationship between neutrophil/lymphocyte ratio with oxidative stress and psychopathology in patients with schizophrenia. *Neuropsychiatr Dis Treat*. 2016;12:1999-2005.
 16. Wang X, Zhang G, Jiang X, Zhu H, Lu Z, Xu L. Neutrophil to lymphocyte ratio in relation to risk of all-cause mortality and cardiovascular events among patients undergoing angiography or cardiac revascularization: a meta-analysis of observational studies. *Atherosclerosis*. 2014;234:206-13.
 17. Shao Q, Chen K, Rha SW, Lim H, Li G, Liu T. Usefulness of Neutrophil/Lymphocyte Ratio as a Predictor of Atrial Fibrillation: A Meta-analysis. *Arch Med Res*. 2015;46:199-206.
 18. Templeton AJ, McNamara MG, Šeruga B, Vera-Badillo FE, Aneja P, Ocaña A, Leibowitz-Amit R, Sonpavde G, Knox JJ, Tran B, Tannock IF, Amir E. Prognostic role of neutrophil-to-lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *J Natl Cancer Inst*. 2014;106:dju124.
 19. Solak Y, Yilmaz MI, Sonmez A, Saglam M, Cakir E, Unal HU, Gok M, Caglar K, Oguz Y, Yenicesu M, Karaman M, Ay SA, Gaipov A, Turk S, Vural A et al. Neutrophil to lymphocyte ratio independently predicts cardiovascular events in patients with chronic kidney disease. *Clin Exp Nephrol*. 2013;17:532-40.
 20. Huang Z, Fu Z, Huang W, Huang K. Prognostic value of neutrophil-to-lymphocyte ratio in sepsis: A meta-analysis. *Am J Emerg Med*. 2020;38:641-7.
 21. Kuyumcu ME, Yesil Y, Oztürk ZA, Kizilarlanoğlu C, Etgül S, Halil M, Ulger Z, Cankurtaran M, Arıoğlu S. The evaluation of neutrophil-lymphocyte ratio in Alzheimer's disease. *Dement Geriatr Cogn Disord*. 2012;34:69-74.
 22. Gökhan S, Ozhasenekler A, Mansur Durgun H, Akil E, Ustündag M, Orak M. Neutrophil lymphocyte ratios in stroke subtypes and transient ischemic attack. *Eur Rev Med Pharmacol Sci*. 2013;17:653-7.
 23. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40:373-83.
 24. Pfeiffer E. A short portable mental status questionnaire for the assessment of organic brain deficit in elderly patients. *J Am Geriatr Soc*. 1975;23:433-41.
 25. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel Index for stroke rehabilitation. *J Clin Epidemiol*. 1989;42:703-9.
 26. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegal AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med*. 1990;113:941-8.
 27. American Psychiatric Association. *DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders*, 4th ed Washington, DC: American Psychiatric Association, 2000.
 28. Wei LA, Fearing MA, Sternberg EJ, Inouye SK. The Confusion Assessment Method: a systematic review of current usage. *J Am Geriatr Soc*. 2008;56:823-30.

29. Hall RJ, Watne LO, Idland AV, Raeder J, Frihagen F, MacLulich AM, Staff AC, Wyller TB, Fekkes D. Cerebrospinal fluid levels of neopterin are elevated in delirium after hip fracture. *J Neuroinflammation*. 2016;13:170.
30. Cape E, Hall RJ, van Munster BC, de Vries A, Howie SE, Pearson A, Middleton SD, Gillies F, Armstrong IR, White TO, Cunningham C, de Rooij SE, MacLulich AM. Cerebrospinal fluid markers of neuroinflammation in delirium: a role for interleukin-1beta in delirium after hip fracture. *J Psychosom Res*. 2014;77:219-25.
31. Egberts A, Wijnbeld EH, Fekkes D, van der Ploeg MA, Ziere G, Hooijkaas H, van der Cammen TJ, Mattace-Raso FU. Neopterin: a potential biomarker for delirium in elderly patients. *Dement Geriatr Cogn Disord*. 2015;39:116-24.
32. Bauer IE, Pascoe MC, Wollenhaupt-Aguiar B, Kapczinski F, Soares JC. Inflammatory mediators of cognitive impairment in bipolar disorder. *J Psychiatr Res*. 2014;56:18-27.
33. Dhabhar FS, Malarkey WB, Neri E, McEwen BS. Stress-induced redistribution of immune cells--from barracks to boulevards to battlefields: a tale of three hormones--Curt Richter Award winner. *Psychoneuroendocrinology*. 2012;37:1345-68.
34. Simone MJ, Tan ZS. The role of inflammation in the pathogenesis of delirium and dementia in older adults: a review. *CNS Neurosci Ther*. 2011;17:506-13.
35. Zenaro E, Pietronigro E, Della Bianca V, Piacentino G, Marongiu L, Budui S, Turano E, Rossi B, Angiari S, Dusi S, Montresor A, Carlucci T, Nani S, Tosadori G, Calciano Letc. Neutrophils promote Alzheimer's disease-like pathology and cognitive decline via LFA-1 integrin. *Nat Med*. 2015;21:880-6.
36. Tanaka T. Factors predicting perioperative delirium and acute exacerbation of behavioral and psychological symptoms of dementia based on admission data in elderly patients with proximal femoral fracture: A retrospective study. *Geriatrics & gerontology international*. 2016;16:821-8.
37. Inoue S, Vasilevskis EE, Pandharipande PP, Girard TD, Graves AJ, Thompson J, Shintani A, Ely EW. The impact of lymphopenia on delirium in ICU patients. *PloS one*. 2015;10:e0126216-e0126216.
38. Azab B, Zaher M, Weiserbs KF, Torbey E, Lacossiere K, Gaddam S, Gobunsuy R, Jadonath S, Baldari D, McCord D, Lafferty J. Usefulness of neutrophil to lymphocyte ratio in predicting short- and long-term mortality after non-ST-elevation myocardial infarction. *Am J Cardiol*. 2010;106:470-6.
39. Turak O, Özcan F, İşleyen A, Başar FN, Gül M, Yılmaz S, Sökmen E, Yüzgeçer H, Lafçi G, Topaloğlu S, Aydoğdu S. Usefulness of neutrophil-to-lymphocyte ratio to predict in-hospital outcomes in infective endocarditis. *Can J Cardiol*. 2013;29:1672-8.
40. de Jager CP, Wever PC, Gemen EF, Kusters R, van Gageldonk-Lafeber AB, van der Poll T, Laheij RJ. The neutrophil-lymphocyte count ratio in patients with community-acquired pneumonia. *PLoS One*. 2012;7:e46561.
41. Núñez J, Núñez E, Bodí V, Sanchis J, Miñana G, Mainar L, Santas E, Merlos P, Rumiz E, Darmofal H, Heatta AM, Llàcer A. Usefulness of the neutrophil to lymphocyte ratio in predicting long-term mortality in ST segment elevation myocardial infarction. *Am J Cardiol*. 2008;101:747-52.
42. Egberts A, Mattace-Raso FU. Increased neutrophil-lymphocyte ratio in delirium: a pilot study. *Clin Interv Aging*. 2017;12:1115-21.
43. Kotfis K, Bott-Olejniak M, Szylińska A, Rotter I. Could Neutrophil-to-Lymphocyte Ratio (NLR) Serve as a Potential Marker for Delirium Prediction in Patients with Acute Ischemic Stroke? A Prospective Observational Study. *Journal of clinical medicine*. 2019;8:1075.
44. Halazun HJ, Mergeche JL, Mallon KA, Connolly ES, Heyer EJ. Neutrophil-lymphocyte ratio as a

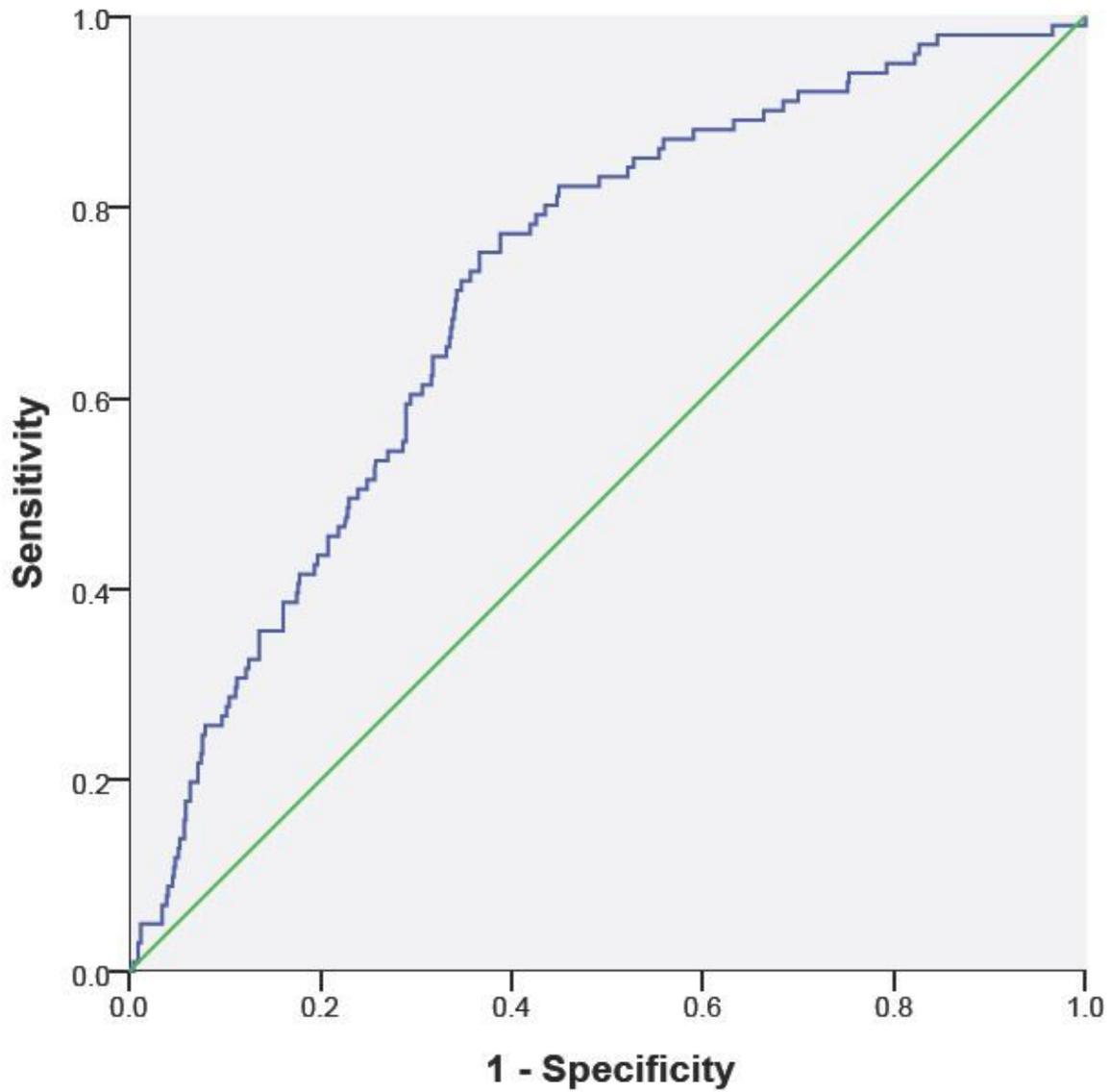
- predictor of cognitive dysfunction in carotid endarterectomy patients. *J Vasc Surg.* 2014;59:768-73.
45. Liu JH, Zhang YJ, Ma QH, Sun HP, Xu Y, Pan CW. Elevated blood neutrophil to lymphocyte ratio in older adults with cognitive impairment. *Arch Gerontol Geriatr.* 2020;88:104041.
46. Cerejeira J, Firmino H, Vaz-Serra A, Mukaetova-Ladinska EB. The neuroinflammatory hypothesis of delirium. *Acta neuropathologica.* 2010;119:737-54.

Figure Titles

Figure 1. Receiver operating characteristics (ROC) of NLR for prediction of delirium

Figures

ROC Curve



Diagonal segments are produced by ties.

Figure 1

Receiver operating characteristics (ROC) of NLR for prediction of delirium