Usefulness of postoperative serum translocator protein as a predictive marker for delirium after breast cancer surgery in elderly women

Guo-Wen Lu, Yi-Er Chou, Wan-Ling Jin and Xiao-Bao Su

Abstract

Objective: Postoperative delirium (POD) has rarely been investigated in breast cancer patients. Herein, we assessed the association between serum levels of the inflammatory biomarker translocator protein (TP) and the occurrence of POD in breast cancer patients.

Methods: In this prospective, observational study, TP levels were detected in preoperative and postoperative serum samples from 152 elderly breast cancer patients, samples from 152 healthy elderly women, and samples from 152 elderly women with benign breast diseases. The relationship between serum TP levels and POD was investigated using multivariate analysis.

Results: TP levels in postoperative patient serum samples were significantly higher than in preoperative patient serum samples and serum from women in the two control groups. Postoperative serum TP levels were independently correlated with serum C-reactive protein levels and the occurrence of POD. Postoperative serum TP levels had a high discriminatory ability for POD under the receiver operating characteristic curve.

Conclusions: Increased postoperative serum TP levels are independently associated with the degree of inflammatory response and the risk of POD in elderly breast cancer patients, substantiating TP as an inflammatory biomarker that can efficiently discriminate POD after breast cancer surgery.

Keywords

Translocator protein, delirium, breast cancer, inflammation, elderly, surgery

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Corresponding author:
Guo-Wen Lu, Department of Thyroid Gland and Breast Surgery, Yinzhou People’s Hospital, 251 Baizhang East Road, Ningbo 315040, China.
Email: ningchennmd@163.com
Introduction

The incidence of cancer has been increasing annually worldwide.1–3 Breast cancer is a common type of cancer that greatly affects women’s health.4–6 Surgery is an important treatment modality for various cancers, including breast cancer.7–9 However, some postoperative complications, including postoperative delirium (POD), are unavoidable during surgery.10–12 Growing data show that POD, which can easily occur in elderly patients, can increase patient mortality and prolong hospital stays.13–16 While there have been many reports of POD in cancer patients,17–19 few studies have investigated POD in breast cancer patients.20,21 Although the mechanisms underlying POD are not fully understood, it is known that cerebral neuronal damage can result in POD. Among the variety of causes, inflammation might be an important process of brain injury.22–24 Thus, we may be able to identify inflammatory biomarkers that can discriminate those at a high risk of POD among breast cancer patients.

Translocator protein 18 kDa (TP) was formerly recognized as a peripheral benzodiazepine receptor.25 It has also been revealed that this receptor is primarily distributed in the brain. Under non-pathological conditions, TP levels are very low in glial cells, but there is accumulating evidence that TP expression increases in parallel with microglial activation. Thus, an imaging technique that traces TP has become a method to quantify neuroinflammation.26,27 Elevated TP levels in peripheral blood have been reported to be highly associated with the severity and outcome of patients with acute ischemic stroke, acute intracerebral hemorrhage, spontaneous subarachnoid hemorrhage, and severe traumatic brain injury.28–31 Thus, TP is considered an inflammatory biomarker that reflects the level of brain injury. However, it is unclear if there is a relationship between circulating TP levels and POD. This study was designed to detect serum TP levels in a group of the elderly breast cancer patients who underwent a surgery, and to further investigate the ability of serum TP to predict POD.

Materials and methods

Study population

We performed this prospective, observational study at Yinzhou People’s Hospital, Ningbo, China between January 2014 and February 2018. The study cohort was composed of three groups of elderly individuals (age ≥65 years old) as follows: (1) elderly female patients with histologically confirmed breast cancer, (2) healthy elderly women (healthy controls), and (3) elderly women with benign breast diseases (benign controls). The exclusion criteria for the breast cancer patients were previous history of any type of cancer, stage 0 (in situ breast cancer) or stage IV disease (multiple cancers, metastatic disease at diagnosis, or distant organ metastasis), recent infection, and a documented history of neurological or psychological diseases (such as dementia, stroke, or delirium). The study protocol was formed based on the World Medical Association Declaration of Helsinki. This study was performed after approval by the ethics committee of Yinzhou People’s Hospital. Written informed consent to participate in the study was obtained from all participants or their relatives.

Assessments

The recorded information included demographic data (e.g., age and body mass index), medical comorbidities (modified Charlson’s Comorbidity Index), surgical risk (American Society of Anesthesiologists rating scale), tumor size, hormone receptor status, lymph node status, histologic grade,
nuclear grade, and tumor-node-metastasis stage. Patients underwent radical mastectomy or modified radical mastectomy, and twice daily during the first 7 postoperative days, we used the Confusion Assessment Method\textsuperscript{32,33} to assess POD. Adjuvant treatments comprised radiotherapy, chemotherapy, and hormone therapy.

**Measurements**

Peripheral blood was drawn from patients via the antecubital vein between 7 and 8 AM 1 day preoperatively and on the first postoperative day. We also obtained blood samples from healthy individuals and controls with benign breast diseases. Blood samples were centrifuged at 3000 \( \times \) g, aliquoted, and frozen at \(-70^\circ\)C until examination. Serum TP levels were quantified in duplicate using a specific enzyme-linked immunosorbent assay kit (Cloud-Clone Corp., Katy, TX, USA) in accordance with the manufacturer’s instructions. Every 3 months, a batch of samples was gauged by the same technician blinded to the patients’ clinical information using the same equipment. The minimum detectable level of TP was 0.127 ng/mL.

**Statistical analysis**

The statistical analysis software used in this study included IBM SPSS Statistics for Windows, version 19.0 (IBM Corp., Armonk, NY, USA) and MedCalc, version 9.6.4.0 (MedCalc Software, Mariakerke, Belgium). This study included two types of data, namely, categorical and continuous data. Categorical data are presented as counts (percentages) and were compared with the Chi-square test or Fisher’s exact test as appropriate. Continuous data were analyzed using the Kolmogorov–Smirnov or Shapiro–Wilk tests to assess the normality of distribution. Normally distributed data were presented as mean (standard deviation), and non-normally distributed data were reported as median (interquartile range [IQR]). Subsequently, a t test, one-way ANOVA, the Mann–Whitney U test, or the Kruskal–Wallis H test were performed for two- or multiple-group comparisons. Bivariate correlation analyses were performed using the Spearman rank correlation test or Pearson correlation test as appropriate; afterwards, a multivariate linear regression model was configured to discern variables that were independently associated with serum TP levels. We also constructed a binary logistic regression model to identify independent predictors of POD. In addition, the odds ratio (OR) and 95% confidence interval (CI) values were reported. Using the receiver operating characteristic (ROC) curve with estimated area under curve (AUC) and 95% CI values, the predictive value of serum TP levels for POD was evaluated and an optimal value was selected, which was used to generate the corresponding sensitivity and specificity values. A two-tailed \( P \) value of \(<0.05\) was designated as the cutoff for statistical significance.

**Results**

**Clinical characteristics of the participants**

In this study, we enrolled 152 elderly women with histologically confirmed breast cancer, 152 healthy elderly women (healthy controls), and 152 elderly women with benign breast diseases (benign controls). There were no statistically significant differences among the three groups regarding age or body mass index. Among the breast cancer patients, the median age was 68 years (range: 65–78 years; IQR: 67–71 years) and the median body mass index was 25.2 kg/m\(^2\) (IQR: 23.2–27.3 kg/m\(^2\); range: 20.2–32.0 kg/m\(^2\)). The median Modified Charlson’s Comorbidity Index was 1 (range: 0–2; IQR: 1–2), and the
American Society of Anesthesiologists rating scale was I for 88 breast cancer patients and II for 64 patients. Tumor sizes were <2 cm in 80 patients and ≥2 cm in 72 patients. Ninety-four patients had tumor-node-metastasis stage I or II disease, and 58 patients had tumor-node-metastasis stage III disease. The lymph node status was negative in 69 patients and positive in 83 patients. The histologic grade was I or II in 77 patients and grade III in 75 patients. Nuclear grade I or II was revealed in 81 breast cancer patients, and 71 were found to be nuclear grade III. A total of 67 and 85 patients presented with negative and positive estrogen receptor status, respectively, and a negative and positive progesterone receptor status was found in 77 and 75 patients, respectively. Among the 152 total elderly breast cancer patients, 30 (19.7%) suffered from POD. The onset of POD ranged from 1 to 5 days after surgery (median: 2 days; IQR: 1–3 days).

Changes in serum TP levels

TP levels were undetectable in all serum samples from healthy controls and benign controls as well as in all preoperative serum samples from breast cancer patients (<0.127 ng/mL); thus, all of these samples were regarded as 0. Postoperative serum TP levels in the elderly breast cancer patients ranged from 0 (undetectable; 113 patients) to 2.209 ng/mL, with a median of 0 ng/mL and an IQR of 0 to 0.172 ng/mL. Obviously, TP levels were substantially higher in the postoperative serum samples from patients than in serum samples from healthy controls and benign controls as well as in preoperative serum samples from the same patients (all \( P < 0.001 \)).

As listed in Table 1, postoperative serum TP levels were closely correlated with tumor size, tumor-node-metastasis stage, lymph node status, histologic grade, nuclear grade, estrogen receptor status, progesterone receptor status, serum C-reactive protein levels, and serum D-dimer levels. Multivariate linear regression analysis showed that postoperative serum TP levels were independently associated with serum C-reactive protein levels (\( t = 4.062, \ P < 0.001 \)) (Figure 1).

| Components                                          | r value | P value |
|-----------------------------------------------------|---------|---------|
| Age (years)                                         | 0.088   | 0.282   |
| Body mass index (kg/m²)                             | -0.061  | 0.457   |
| Modified Charlson’s Comorbidity Index               | 0.128   | 0.115   |
| American Society of Anesthesiologists rating scale (I/II) | 0.085   | 0.298   |
| Tumor size (<2 cm/≥2 cm)                            | 0.210   | 0.009   |
| Tumor-node-metastasis stage (I+II/III)              | 0.442   | <0.001  |
| Lymph node status (negative/positive)               | 0.249   | 0.002   |
| Histologic grade (I+II/III)                         | 0.280   | <0.001  |
| Nuclear grade (I+II/III)                            | 0.187   | 0.021   |
| Estrogen receptor status (negative/positive)        | 0.224   | 0.006   |
| Progesterone receptor status (negative/positive)    | 0.180   | 0.027   |
| Serum C-reactive protein levels (mg/L)              | 0.448   | <0.001  |
| Blood white blood cell count (×10^9/L)              | 0.148   | 0.068   |
| Serum D-dimer levels (mg/L)                         | 0.219   | 0.007   |

Bivariate correlation was analyzed using Spearman rank correlation test.
POD prediction ability of serum TP levels

Postoperative serum TP levels were remarkably elevated in patients who developed POD compared with those who did not (Figure 2). Using ROC curve analysis, we found that postoperative serum TP levels exhibited a significantly high discriminatory ability for patients at risk of POD (Figure 3); moreover, a cutoff value of 0.385 ng/mL was found to differentiate between patients with a risk of developing POD and those without a risk of POD. This TP cutoff value presented a sensitivity of 70.0% and a specificity of 95.1%. As shown in Tables 2 and 3, compared with patients who did not present a risk of POD, those who developed POD tended to be older, were more likely to have an elevated tumor-node-metastasis stage and a positive lymph node status, were more prone to have an increased histologic and nuclear grade, had significantly increased serum C-reactive protein levels, white blood cell counts, and serum D-dimer levels, as well as substantially increased postoperative serum TP levels (>0.385 ng/mL). When these variables were incorporated into a binary multivariate logistic regression model, we found that age and postoperative serum TP levels >0.385 ng/mL were independently associated with the occurrence of POD (Table 4).

Discussion

To the best of our knowledge, this is the first study to investigate serum TP levels...
| Components                                                                 | Presence of POD (n = 30) | Absence of POD (n = 122) | P value |
|---------------------------------------------------------------------------|--------------------------|---------------------------|---------|
| Age (years)                                                               | 71 (68–73)               | 67 (66–70)                | <0.001  |
| Body mass index (kg/m²)                                                  | 24.2 (22.6–27.1)         | 25.1 (23.4–27.3)          | 0.383   |
| Modified Charlson’s Comorbidity Index                                    | 1 (1–2)                  | 1 (0–2)                   | 0.200   |
| American Society of Anesthesiologists rating scale (I+II)                | 14/16                    | 74/48                     | 0.164   |
| Tumor size (<2 cm/≥2 cm)                                                 | 13/17                    | 67/55                     | 0.255   |
| Tumor-node-metastasis stage (I+II/III)                                    | 12/18                    | 82/40                     | 0.006   |
| Lymph node status (negative/positive)                                     | 8/22                     | 61/61                     | 0.021   |
| Histologic grade (I+II/III)                                              | 9/21                     | 68/54                     | 0.012   |
| Nuclear grade (I+II/III)                                                 | 11/19                    | 70/52                     | 0.042   |
| Estrogen receptor status (negative/positive)                             | 13/17                    | 54/68                     | 0.927   |
| Progesterone receptor status (negative/positive)                         | 14/16                    | 63/59                     | 0.626   |
| Serum C-reactive protein levels (mg/L)                                   | 31.7 (24.6–35.0)         | 26.5 (19.4–31.7)          | 0.008   |
| Blood white blood cell count (×10⁹/L)                                    | 9.1 (7.0–11.0)           | 7.3 (5.5–9.4)             | 0.004   |
| Serum D-dimer levels (mg/L)                                               | 3.3 (2.3–4.5)            | 2.3 (1.7–2.5)             | 0.002   |
| Postoperative serum translocator protein levels >0.385 ng/mL              | 20 (66.7%)               | 8 (7.1%)                  | <0.001  |

Data are reported as median (interquartile range) or counts (percentage) as appropriate and were compared with the Mann–Whitney U test, chi-square test, or Fisher exact test as indicated. n denotes the number of patients.

| Components                                                                 | Odds ratio (95% confidence interval) | P value |
|---------------------------------------------------------------------------|--------------------------------------|---------|
| Age (years)                                                               | 1.235 (1.094–1.395)                 | 0.001   |
| Body mass index (kg/m²)                                                  | 0.932 (0.799–1.089)                 | 0.376   |
| Modified Charlson’s Comorbidity Index                                    | 1.479 (0.847–2.584)                 | 0.169   |
| American Society of Anesthesiologists rating scale (I/II)                | 1.762 (0.789–3.937)                 | 0.167   |
| Tumor size (<2 cm/≥2 cm)                                                 | 1.218 (0.548–2.710)                 | 0.629   |
| Tumor-node-metastasis stage (I+II/III)                                    | 3.075 (1.351–6.999)                 | 0.007   |
| Lymph node status (negative/positive)                                     | 2.750 (1.137–6.654)                 | 0.025   |
| Histologic grade (I+II/III)                                              | 2.938 (1.245–6.935)                 | 0.014   |
| Nuclear grade (I+II/III)                                                 | 2.325 (1.019–5.304)                 | 0.045   |
| Estrogen receptor status (negative/positive)                             | 1.185 (0.530–2.650)                 | 0.679   |
| Progesterone receptor status (negative/positive)                         | 1.220 (0.548–2.717)                 | 0.626   |
| Serum C-reactive protein levels (mg/L)                                   | 1.067 (1.016–1.120)                 | 0.009   |
| Blood white blood cell count (×10⁹/L)                                    | 1.249 (1.083–1.440)                 | 0.002   |
| Serum D-dimer levels (mg/L)                                               | 1.681 (1.221–2.316)                 | 0.001   |
| Postoperative serum translocator protein levels >0.385 ng/mL              | 28.500 (10.032–80.962)              | <0.001  |
in breast cancer patients with POD. Although many papers\textsuperscript{17–19} have reported POD cases in cancer, few reports have investigated POD in only breast cancer patients.\textsuperscript{20,21} Therefore, our data regarding POD in breast cancer are novel. The main findings of our study are that: (1) there was a 19.7\% incidence rate of POD in this cohort of breast cancer patients; (2) compared with the serum from healthy controls and benign controls as well as preoperative serum samples from patients, TP levels were significantly increased in postoperative serum samples from patients; (3) postoperative serum TP levels were significantly higher in patients at risk of POD than in those not experiencing POD; (4) postoperative serum TP levels were independently correlated with serum C-reactive protein levels by multivariate linear regression analysis; (5) postoperative serum TP levels were highly predictive of POD; and (6) postoperative serum TP levels, which were identified as a categorical variable, in addition to age were the two independent predictors of POD in this cohort of breast cancer patients. Taken together, these findings suggest that TP could be an inflammatory biomarker that can distinguish POD in elderly breast cancer patients.

Although postoperative inflammatory brain injury is an important mechanism for the occurrence and development of POD,\textsuperscript{22–24} the biological functions of TP in the central nervous system remain to be explored. However, there is significant evidence that TP can be an inflammatory biomarker that reflects the inflammatory status of various acute brain injury diseases, such as acute intracerebral hemorrhage, ischemic stroke, acute traumatic brain injury, and spontaneous subarachnoid hemorrhage.\textsuperscript{28–31} This study showed that postoperative serum TP levels were significantly elevated compared with preoperative serum TP levels in breast cancer patients and fasting serum TP levels in healthy and benign controls. Intriguingly, serum C-reactive protein levels were also independently correlated with postoperative serum TP levels after correcting for other possible confounding factors, such as tumor size and histological type. These results indicated that postoperative brain injuries might exist in breast cancer patients.

In this study, we found that the POD incidence of breast cancer patients was 19.7\%. Disappointingly, owing to the paucity of previous data regarding POD in breast cancer patients, we could not make

| Components | Odds ratio (95\% confidence interval) | P value |
|------------|---------------------------------------|---------|
| Age (years) | 1.374 (1.130–1.671)                   | 0.001   |
| Tumor-node-metastasis stage (I+II/III) | 1.421 (0.473–4.272)                   | 0.531   |
| Lymph node status (negative/positive) | 1.822 (0.599–5.545)                   | 0.291   |
| Histologic grade (I+II/III) | 1.367 (0.469–3.983)                   | 0.567   |
| Nuclear grade (I+II/III) | 1.851 (0.662–5.172)                   | 0.240   |
| Serum C-reactive protein levels (mg/L) | 1.043 (0.984–1.106)                   | 0.152   |
| Blood white blood cell count ($\times 10^9$/L) | 0.980 (0.904–1.063)                   | 0.625   |
| Serum D-dimer levels (mg/L) | 1.745 (0.461–6.602)                   | 0.412   |
| Postoperative serum translocator protein levels $>0.385$ ng/mL | 33.343 (11.223–196.164) | $<0.001$ |
a comparison of the POD incidence from previous reports. The other finding of this study was that postoperative serum TP levels were significantly raised in patients at high risk of POD compared with patients who did not suffer from POD. We hypothesize that neuroinflammation might be a factor that results in POD in breast cancer patients. The reasons for neuroinflammation causing POD may include intraoperative ischemic and hypoxic brain injury, to which the elderly are increasingly susceptible, however, the actual pathogenesis of POD needs to be explored in future studies of breast cancer patients.

In this study, we further clarified the predictive value of serum TP levels for POD in this group of cancer breast patients. In accordance with the AUC (0.823), serum TP levels had a medium-high predictive value for POD. Using a multivariate logistic regression analysis, age and serum TP levels were highly associated with POD among breast cancer patients. Clearly, age is the most relevant determinant for POD in a variety of diseases. Thus, it would be interesting for serum TP levels to be an independent predictor for POD only in elderly breast cancer patients. This interpretation is based on TP being a well-known candidate for neuroinflammation. Although such an explanation needs to be verified in a larger cohort, this finding might indicate that serum TP could be used as a neuroinflammatory biomarker to predict POD in elderly breast cancer patients.

In conclusion, our data showed that increased postoperative serum TP levels were closely associated with serum C-reactive protein levels and independently predicted POD among elderly women with breast cancer. Serum TP levels exhibited a high discriminatory capability, which substantialized postoperative serum TP as a promising inflammatory biomarker to distinguish elderly breast cancer patients who are at risk of POD.

**Abbreviations**

AUC, area under curve; CI, confidence interval; IQR, interquartile range; OR, odds ratio; POD, postoperative delirium; ROC, receiver operating characteristic; TP, translocator protein.

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**Data availability statement**

The data that support the findings of this study are available upon request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

**Declaration of conflicting interest**

The authors declare that there is no conflict of interest.

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**ORCID iD**

Guo-Wen Lu https://orcid.org/0000-0001-7800-3373

**References**

1. Poddar A, Aranha R, Royam MM, et al. Incidence, prevalence, and mortality associated with head and neck cancer in India: protocol for a systematic review. Indian J Cancer 2019; 56: 101–106.

2. Ha Chung B, Horie S and Chiong E. The incidence, mortality, and risk factors of prostate cancer in Asian men. Prostate Int 2019; 7: 1–8.

3. Wu C, Li M, Meng H, et al. Analysis of status and countermeasures of cancer incidence and mortality in China. Sci China Life Sci 2019; 62: 640–647.
4. Adeloye D, Sowunmi OY, Jacobs W, et al. Estimating the incidence of breast cancer in Africa: a systematic review and meta-analysis. *J Glob Health* 2018; 8: 010419.

5. Power EJ, Chin ML and Haq MM. Breast cancer incidence and risk reduction in the Hispanic population. *Cureus* 2018; 10: e2235.

6. Spronk I, Schellevis FG, Burgers JS, et al. Incidence of isolated local breast cancer recurrence and contralateral breast cancer: a systematic review. *Breast* 2018; 39: 70–79.

7. Murugappan K, Saboo A, Kuo L, et al. Paradigm shift in the local treatment of breast cancer: mastectomy to breast conservation surgery. *Gland Surg* 2018; 7: 506–519.

8. Chatterjee A. Long term effects of modern breast cancer surgery. *Gland Surg* 2018; 7: 366–370.

9. Mitchell MP and Sharma P. The use of surgery and radiotherapy as treatment of regional nodes in breast cancer patients. *Oncology (Williston Park)* 2018; 32: e52–e64.

10. Gockel I, Niebisch S, Ahlbrand CJ, et al. Risk and complication management in esophageal cancer surgery: a review of the literature. *Thorac Cardiovasc Surg* 2018; 64: 596–605.

11. Mak A. Orthopedic surgery and its complication in systemic lupus erythematosus. *World J Orthop* 2014; 5: 38–44.

12. Tebo CC, Evins AI, Christos PJ, et al. Evolution of cranial epilepsy surgery complication rates: a 32-year systematic review and meta-analysis. *J Neurosurg* 2014; 120: 1415–1427.

13. Lipowski ZJ. Delirium in the elderly patient. *N Engl J Med* 1989; 320: 578–582.

14. He Z, Cheng H, Wu H, et al. Risk factors for postoperative delirium in patients undergoing microvascular decompression. *PLoS One* 2019; 14: e0215374.

15. Abbott TEF and Pearse RM. Depth of anesthesia and postoperative delirium. *JAMA* 2019; 321: 459–460.

16. Kang SY, Seo SW and Kim JY. Comprehensive risk factor evaluation of postoperative delirium following major surgery: clinical data warehouse analysis. *Neurol Sci* 2019; 40: 793–800.

17. Shim EJ, Noh HL, Lee KM, et al. Trajectory of severity of postoperative delirium symptoms and its prospective association with cognitive function in patients with gastric cancer: results from a prospective observational study. *Support Care Cancer* 2019; 27: 2999–3006. doi: 10.1007/s00520-018-4604-4.

18. Mosk CA, van Vugt JLA, de Jonge H, et al. Low skeletal muscle mass as a risk factor for postoperative delirium in elderly patients undergoing colorectal cancer surgery. *Clin Interv Aging* 2018; 13: 2097–2106.

19. Honda S, Furukawa K, Nishiwaki N, et al. Risk factors for postoperative delirium after gastrectomy in gastric cancer patients. *World J Surg* 2018; 42: 3669–3675.

20. Cacho-Díaz B, Lorensana-Mendoza NA, Reyes-Soto G, et al. Neurologic manifestations of elderly patients with cancer. *Aging Clin Exp Res* 2019; 31: 201–207.

21. Choi JY, Yoon SJ, Kim SW, et al. Prediction of postoperative complications using multidimensional frailty score in older female cancer patients with American society of anesthesiologists physical status class 1 or 2. *J Am Coll Surg* 2015; 221: 652–660.

22. Vasunilashorn SM, Dillon ST, Inouye SK, et al. High C-reactive protein predicts delirium incidence, duration, and feature severity after major noncardiac surgery. *J Am Geriatr Soc* 2017; 65: e109–e116.

23. Neerland BE, Hall RJ, Seljeflot I, et al. Associations between delirium and preoperative cerebrospinal fluid C-reactive protein, Interleukin-6, and Interleukin-6 receptor in individuals with acute hip fracture. *J Am Geriatr Soc* 2016; 64: 1456–1463.

24. Cerejeira J, Nogueira V, Luís P, et al. The cholinergic system and inflammation: common pathways in delirium pathophysiology. *J Am Geriatr Soc* 2012; 60: 669–675.

25. Papadopoulos V, Baraldi M, Guilarte TR, et al. Translocator protein (18 kDa): new nomenclature for the peripheral-type benzodiazepine receptor based on its structure and molecular function. *Trends Pharmacol Sci* 2006; 27: 402–409.

26. Karlstetter M, Nothdurfter C, Aslanidis A, et al. Translocator protein (18 kDa) (TSPO)
is expressed in reactive retinal microglia and modulates microglial inflammation and phagocytosis. *J Neuroinflammation* 2014; 11: 3.

27. Liu GJ, Middleton RJ, Hatty CR, et al. The 18 kDa translocator protein, microglia and neuroinflammation. *Brain Pathol* 2014; 24: 631–653.

28. Chen WH, Yeh HL, Tsao CW, et al. Plasma translocator protein levels and outcomes of acute ischemic stroke: a pilot study. *Dis Markers* 2018; 2018: 9831079.

29. Bonsack F, Foss CA, Arbab AS, et al. [125I]IodoDPA-713 binding to 18 kDa translocator protein (TSPO) in a mouse model of intracerebral hemorrhage: implications for neuroimaging. *Front Neurosci* 2018; 12: 66.

30. Thomas C, Vercouillie J, Doméné A, et al. Detection of neuroinflammation in a rat model of subarachnoid hemorrhage using [18F]DPA-714 PET imaging. *Mol Imaging* 2016; 15: pii: 1536012116639189. doi: 10.1177/1536012116639189.

31. Luo LF, Weng JF, Cen M, et al. Prognostic significance of serum translocator protein in patients with traumatic brain injury. *Clin Chim Acta* 2019; 488: 25–30.

32. Ely EW, Inouye SK, Bernard GR, et al. Delirium in mechanically ventilated patients: validity and reliability of the confusion assessment method for the intensive care unit (CAM-ICU). *JAMA* 2001; 286: 2703–2710.

33. Ely EW, Margolin R, Francis J, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med* 2001; 29: 1370–1379.

34. Nie H, Zhao B, Zhang YQ, et al. Pain and cognitive dysfunction are the risk factors of delirium in elderly hip fracture Chinese patients. *Arch Gerontol Geriatr* 2012; 54: e172–e174.

35. Lundstrom M, Edlund A, Bucht G, et al. Dementia after delirium in patients with femoral neck fractures. *J Am Geriatr Soc* 2003; 51: 1002–1006.

36. Kratz T, Heinrich M, Schlauß E, et al. Preventing postoperative delirium. *Dtsch Arztebl Int* 2015; 112: 289–296.

37. Kumar AK, Jayant A, Arya VK, et al. Delirium after cardiac surgery: a pilot study from a single tertiary referral center. *Ann Card Anaesth* 2017; 20: 76–82.

38. Oe S, Togawa D, Yamato Y, et al. Preoperative age and prognostic nutritional index are useful factors for evaluating postoperative delirium among patients with adult spinal deformity. *Spine (Phila Pa 1976)* 2019; 44: 472–478.

39. Kubota K, Suzuki A, Ohde S, et al. Age is the most significantly associated risk factor with the development of delirium in patients hospitalized for more than five days in surgical wards: retrospective cohort study. *Ann Surg* 2018; 267: 874–877.

40. Pinho C, Cruz S, Santos A, et al. Postoperative delirium: age and low functional reserve as independent risk factors. *J Clin Anesth* 2016; 33: 507–513.