

CLINICAL RESEARCH

## S100B level and cognitive dysfunction after robotic-assisted laparoscopic radical prostatectomy procedures: a prospective observational study



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### KEYWORDS

S100B protein;  
Postoperative  
cognitive  
dysfunction;  
Robotic assisted  
laparoscopic radical  
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### Abstract

**Background:** The present study investigated the association between Postoperative Cognitive Dysfunction (POCD) and increased serum S100B level after Robotic-Assisted Laparoscopic Radical Prostatectomy (RALRP).

**Methods:** The study included 82 consecutive patients who underwent RALRP. Serum S100B levels were determined preoperatively, after anesthesia induction, and at 30 minutes and 24 hours postoperatively. Cognitive function was assessed using neuropsychological testing preoperatively, and at 7 days and 3 months postoperatively.

**Results:** Twenty four patients (29%) exhibited POCD 7 days after surgery, and 9 (11%) at 3 months after surgery. Serum S100B levels were significantly increased at postoperative 30 minutes and 24 hours in patients displaying POCD at postoperative 7 days ( $p=0.0001$  for both) and 3 months ( $p=0.001$  for both) compared to patients without POCD. Duration of anesthesia was also significantly longer in patients with POCD at 7 days and 3 months after surgery compared with patients without POCD ( $p=0.012$ ,  $p=0.001$ , respectively), as was duration of Trendelenburg ( $p=0.025$ ,  $p=0.002$ , respectively). Composite Z score in tests performed on day 7 were significantly correlated with duration of Trendelenburg and duration of anesthesia ( $p=0.0001$  for both).

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**PALAVRAS-CHAVE**  
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**Conclusions:** S100B increases after RALRP and this increase is associated with POCD development. Duration of Trendelenburg position and anesthesia contribute to the development of POCD.

**Trial Registry Number:** Clinicaltrials.gov (N° NCT03018522).

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## Nível de S100B e disfunção cognitiva após prostatectomia radical laparoscópica assistida por robô: estudo observacional prospectivo

### Resumo

**Introdução:** O presente estudo investigou a associação entre Disfunção Cognitiva Pós-Operatória (DCPO) e aumento do nível sérico de S100B após Prostatectomia Radical Laparoscópica Assistida por Robô (PRLAR).

**Métodos:** O estudo incluiu 82 pacientes consecutivos submetidos a PRLAR. Os níveis séricos de S100B foram determinados: no pré-operatório, após indução anestésica, e aos 30 minutos e 24 horas do pós-operatório. A função cognitiva foi avaliada com testes neuropsicológicos no pré-operatório, no 7º dia pós-operatório (7DPO) e aos 3 meses após a cirurgia (3MPO).

**Resultados:** Observamos 24 pacientes (29%) com DCPO no 7DPO e 9 pacientes com DCPO (11%) após 3 meses da cirurgia. Quando comparados com os pacientes sem DCPO, os níveis séricos de S100B estavam significativamente aumentados aos 30 minutos e às 24 horas do pós-operatório nos pacientes que apresentaram DCPO no 7DPO ( $p=0,0001$  para os dois momentos) e 3 meses após a cirurgia ( $p=0,001$  para os dois momentos) A duração anestésica também foi significativamente maior em pacientes com DCPO no 7DPO e 3MPO em comparação com pacientes sem DCPO ( $p=0,012$ ,  $p=0,001$ , respectivamente), assim como a duração da posição de Trendelenburg ( $p=0,025$ ,  $p=0,002$ , respectivamente). O escore Z composto nos testes realizados no 7DPO foi significativamente correlacionado com a duração da posição de Trendelenburg e a duração da anestesia ( $p=0,0001$  para ambos).

**Conclusão:** S100B aumenta após PRLAR e o aumento está associado ao desenvolvimento de DCPO. A duração anestésica e o tempo decorrido em posição de Trendelenburg contribuem para o desenvolvimento de DCPO.

**Número de registro do estudo:** Clinicaltrials.gov (n° NCT03018522)

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## Introduction

Technical advances in surgery have led to the increasingly widespread use of minimally invasive techniques in radical prostatectomy. Robotic-Assisted Laparoscopic Radical Prostatectomy (RALRP) is preferred in many centers because it circumvents the disadvantages of conventional laparoscopy, reduces short-term complications, and provides better functional results compared to the conventional technique.<sup>1</sup>

Early Postoperative Cognitive Dysfunction (POCD), confusion, and delirium are common after major surgery in older adults.<sup>2,3</sup> Patients undergoing RALRP are usually elderly, and protecting the critical balance between cerebral oxygen supply and demand during this procedure is important because impaired cerebral oxygenation is associated with postoperative cognitive decline.<sup>4-6</sup> Patients must be positioned in the steep Trendelenburg position for several hours

during robotic-assisted prostatectomy. The combination of Trendelenburg position and peritoneal inflation with carbon dioxide increases airway pressure, reduces pulmonary compliance, induces atelectasis, and causes potentially adverse cardiovascular and neurophysiological changes.<sup>7</sup> This combination can also increase Intracranial Pressure (ICP), which may in turn cause cerebral edema due to reduced venous drainage of the brain.<sup>8</sup> These changes may result in POCD.

S100B is a calcium-binding protein produced by astrocytes and found both extra- and intracellularly in brain tissue. The physiological role of S100B is to enhance interaction between neurons and glial cells.<sup>9</sup> S100B may be a potential biochemical marker for POCD because this protein is usually released into the blood following neural damage due to impaired permeability of the blood-brain barrier.

The aim of the present study was to investigate the association between POCD and increased serum S100B levels after RALRP.

## Methods

This study was carried out in accordance with the Declaration of Helsinki, approved by the ethics committee of Antalya Training and Research Hospital (approval n° 64/2), and was also registered in the Clinicaltrials.gov clinical trials registry (n° NCT03018522). Written informed consent was obtained from all patients. The STROBE (Strengthening of Reporting of Observational Studies in Epidemiology) guidelines were followed when reporting this study.

Patients who underwent RALRP, were over 50 years old, had a body mass index between 18 and 25 kg.m<sup>-2</sup>, and were class I, II, or III according to the American Society of Anesthesiologists (ASA) physical status classification system were included in the study. Exclusion criteria were history of neurological deficit (symptomatic stroke, hemorrhage, transient ischemic attack) or other neurologic disorders (epilepsy, trauma, intra- or extracranial malignancy), psychiatric diseases (schizophrenia or depressive disorder), alcoholism or any other drug dependence, severe hearing or visual impairment, any other comorbidities which would preclude neuropsychological tests, and preexisting cognitive impairment (score < 25 on the Mini Mental State Examination [MMSE]).

## Cognitive assessment

The MMSE is a brief test used to quantitatively evaluate cognitive functions during a standard neuropsychiatric examination. The test consists of 11 questions with a maximum score of 30 points. The MMSE includes orientation, working memory, arithmetic calculations, recall, and language tests. Scores under 25 points indicate cognitive impairment.<sup>10,11</sup> In the current study, the MMSE was used only before surgery for preoperative cognitive impairment screening, and participants who obtained scores below 25 points were excluded.

We designed a neurocognitive assessment protocol to evaluate general cognitive function and identify patients with POCD. This protocol was repeated for all patients the day before surgery and at 7 days and 3 months after surgery. A single trained investigator who was not involved in the intraoperative management of the patients performed all cognitive assessments.

Based on a consensus statement,<sup>12</sup> we assessed cognitive function using a battery of 7 neuropsychological tests: Rey Auditory Verbal Learning Test (delayed recall), Trail Making Test (Parts A and B), Digit Span Test (forward and backward), and Grooved Pegboard Test (dominant and non-dominant hands). To determine the normal reference value of cognitive functions, 20 healthy individuals matched for sex, age, and education level, and having no significant mental or somatic disorders or recent surgical history were recruited as a control group. Cognitive functions were assessed 3 times (the first interval was 7 days and the second interval was 3 months), and the standard deviation of the baseline score was calculated. Learning effects, which occur in

repeated neuropsychological tests, were also calculated.<sup>11</sup> The patients in the study group were divided into the POCD and non-POCD groups according to the International Study of Postoperative Cognitive Dysfunction guidelines.<sup>11</sup> To identify cognitive dysfunction, the baseline score and learning effect were subtracted from the test score and the difference was divided by the standard deviation of the score in the control group. This result was called the Z score. Z score was calculated for each test and POCD was defined as a Z score greater than 1.96 in at least 2 of the 7 tests, and/or a composite Z score greater than 1.96.<sup>2,13</sup>

Memory was evaluated using the Rey Auditory Verbal Learning Test (RAVLT). This test assesses short-term auditory/verbal memory, retroactive and proactive interference, presence of confabulation or confusion in memory processes, retention of information, and differences between learning and retrieval. The RAVLT consists of a list of 15 words to be memorized (List A). The list is read aloud in the same order 5 consecutive times. After the fifth reading, participants are presented with a distracter list (List B) with 15 different concrete nouns, followed by a free-recall test from List B. After a 20-minute interval, participants are asked again to recall the words from List A (delayed recall) and are evaluated based on the number of words recalled and the number of errors made for each presentation.<sup>14</sup>

The Trail Making Test (TMT) assesses speed, visuospatial skills, general fluid cognitive abilities, cognitive flexibility, set-switching, motor skills, and dexterity. The test consists of two parts (TMT-a and TMT-b). In TMT-a, the participant is instructed to draw a line connecting encircled numbers in an ordered sequence (1, 2, 3,...26) as quickly as possible without lifting the pen from the surface of the paper. In TMT-b, the participant connects a series of circles containing either a number or letter in alternating sequence (1, A, 2, B,...13). Each part is scored according to the total time to completion and number of errors.<sup>15</sup>

The Digit Span Test was administered to assess concentration, attention, and immediate memory. The Digit Span Forward (DSF) is a measure for short-term memory that primarily activates the phonological loop. The Digit Span Backward (DSB) shows the dynamic relationship between passive storage and active manipulation or transformation of information held in the memory (the ability to hold information in the mind and work with it). The DSF consists of 12 sequences of digits varying in length from 3 to 8 digits (2 sequences of each length). Digits are announced by the researcher at a rate of approximately 1 digit per second. After completion of the digit sequence, participants are asked to write down the sequence. The DSB consists of 12 sequences varying in length from 2 to 7 digits (2 sequences of each length) and after completion of the sequence by the researcher, participants are asked to write down the sequence backwards, starting with the last number announced.<sup>16</sup>

Motor coordination and dexterity were evaluated using the Grooved Pegboard Test. In this test, participants use their dominant hand to correctly insert pegs into a pegboard in a certain sequence or pattern. Time to completion is recorded and the process is repeated with their nondominant hand.<sup>17</sup>

## Serum S100B analysis

Serum levels of S100B were determined from venous blood samples collected before surgery, after anesthesia induction, and at 30 minutes and 24 hours after surgery. Samples were collected in sterile vacuum tubes without anticoagulants and centrifuged at 3000 rpm for 20 minutes to obtain the serum, which was stored at  $-80^{\circ}\text{C}$ . S100B levels were measured using an Enzyme-Linked Immunosorbent Assay (ELISA) kit (Neobioscience Technology Company, Beijing, China) according to the manufacturer's protocol.

## Anesthesia

On arrival in the operating room, a 16G peripheral venous catheter was placed. Patients were under standard monitoring including invasive blood pressure (via 20G catheter in radial artery), 5-lead electrocardiography, pulse oximetry, end tidal  $\text{CO}_2$ , Bispectral Index (BIS), regional cerebral oxygen saturation, urinary output, and body core temperature. In all patients, general anesthesia was induced with intravenous (IV) midazolam  $0.1\text{ mg}\cdot\text{kg}^{-1}$ , propofol  $1.5\text{ mg}\cdot\text{kg}^{-1}$ , fentanyl  $2\text{ }\mu\text{g}\cdot\text{kg}^{-1}$ , and rocuronium  $0.6\text{ mg}\cdot\text{kg}^{-1}$ . All patients were intubated with a 7.5-mm or 8-mm inner diameter endotracheal tube. Anesthesia was maintained with 50% air and 0.8–1.5 age-adjusted minimum alveolar anesthetic concentration of desflurane calculated by the monitoring software (Primus Drager, Luebeck, Germany) with positive pressure ventilation in a circle system. For all patients, depth of anesthesia was monitored with the Patient State Index (PSI<sup>TM</sup>) (SedLine<sup>®</sup>, Masimo, Irvine, CA, USA). PSI value was kept between 25 and 50 and the maintenance dosage was adjusted if necessary. Repeated injections of fentanyl and rocuronium were administered when necessary. End tidal  $\text{CO}_2$  was maintained between 30 and 35 mmHg by ventilatory parameters adjusted after creating  $\text{CO}_2$  pneumoperitoneum. Fasting fluid requirement of the patient was replaced as per standard guidelines, but the intraoperative maintenance fluid was restricted to  $2\text{ mL}\cdot\text{kg}^{-1}\cdot\text{h}^{-1}$  until completion of the vesicourethral anastomosis, after which IV fluid administration was made as per standard fluid management guidelines based on replacement of fluid deficit, third-space fluid loss, and blood loss. When mean arterial pressure decreased to 80% of the preinduction value, a 5–10 mg bolus of ephedrine was administered.

Regional Oxygen Saturation ( $\text{rSO}_2$ ) of blood in the cerebral cortex was measured using the regional oximetry system (O3<sup>TM</sup>, Masimo, Irvine, CA, USA). Bilateral Near-Infrared Spectroscopy (NIRS) sensors were attached to the patient's forehead prior to preoxygenation and anesthesia induction to calculate baseline values. Cerebral oximetry was continuously measured and recorded for the duration of the operative procedure and discontinued once the patient left the operating room.

A custom-made foam pillow placed under the head and cross-shoulder braces were used to prevent the patient from sliding. The patient's legs were placed in urological leg holders for modified lithotomy position. After positioning the patient, the abdominal cavity was insufflated with  $\text{CO}_2$  to a pressure of 10 mmHg and the patient was placed in mild Trendelenburg position, after which the tro-

car cannulas were placed. Finally, the patient's position was gradually adjusted to the  $45^{\circ}$  Trendelenburg position over 5 minutes. All operations were performed with the same degree of Trendelenburg. The surgeon performed the procedure with the Da Vinci Robot Surgical System (Intuitive Surgical, Sunnyvale, CA, USA) using a transperitoneal approach. All procedures were performed by the same two senior surgeons. At the end of the procedure, the table was brought back to normal position and the pneumoperitoneum was released. All patients were awakened in the operating theater and then moved to the postanesthesia care unit.

Postoperative analgesia was maintained by IV paracetamol ( $10\text{--}15\text{ mg}\cdot\text{kg}^{-1}$ ) every 8 hours and IV tramadol ( $1\text{ mg}\cdot\text{kg}^{-1}$ ) if required.

Criteria for discharge from the postanesthesia care unit were that patients must be awake, cooperative, hemodynamically stable, have an acceptable respiratory pattern, and show recovery of motor functions.

## Statistical analysis

Based on the estimated profile of sensitivity and specificity of the association between serum S100B level and POCD, sample size was estimated as 80 patients to estimate sensitivity and specificity of 70% with an error of 10%, confidence interval of 95%, and power of 80%.

Statistical analysis was performed using SPSS version 21 statistical software (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean  $\pm$  standard deviation with range, and categorical data as absolute frequencies and percentages.

All numerical data were tested for normal distribution using Kolmogorov-Smirnov test. Parametric and nonparametric continuous data were analyzed using ANOVA or Kruskal-Wallis test. Variables showing significant differences were further analyzed using Bonferroni's multiple comparison test or Mann-Whitney test with correction for multiple comparisons. Linear regression analysis was used to assess the relationship between postoperative plasma biomarkers and change in postoperative cognitive scores. Paired Student's *t*-test was used to assess changes in neurocognitive measures. Correlation analyses were performed using Pearson's or Spearman's rank sum correlation. All confidence intervals were constructed with 95% statistical confidence. A *p*-value less than 0.05 was considered statistically significant.

## Results

Eighty-nine patients were enrolled in the study. Seven patients were excluded because they refused to take the postoperative cognitive tests. Data from the remaining 82 patients were analyzed. There were no significant differences between the study group and healthy control group in terms of age, body mass index, education level, ASA status, or cognitive functions at baseline. The characteristics of the patients and controls are shown in Table 1.

POCD was detected in 24 patients (29%) on postoperative day 7 and in 9 patients (11%) at postoperative 3 months. The mean ages of the patients with and without POCD on postoperative day 7 were  $66 \pm 7.2$  and  $60.6 \pm 7.6$

**Table 1** Patients' characteristics and baseline test scores (values are expressed as mean±SD [range] or number and percentage).

	Study Group (n = 82)	Control Group (n = 20)	p-value
Age, years	62.2 ± 7.8	63.9 ± 5.1	0.365
Body mass index, kg.m <sup>-2</sup>	26.1 ± 3.9	25.4 ± 4.6	0.546
Education, years	10 (5–15)	9.8 (5–15)	0.487
Duration of Trendelenburg, min	237 ± 55	-	-
Duration of anesthesia, min	328 ± 62	-	-
Hospital stay, days	6 ± 2	-	-
<b>ASA status</b>			
I, n (%)	8 (10)	2 (10)	0.489
II, n (%)	54 (66)	14 (70)	0.517
III, n (%)	20 (27)	4 (20)	0.356
<b>Comorbidity</b>			
Arterial hypertension, n (%)	28 (34)	9 (45)	0.125
Diabetes mellitus, n (%)	31 (38)	8 (40)	0.273
COPD, n (%)	7 (8)	2 (10)	0.132
CRF, n (%)	3 (3)	0 (0)	0.223
Smoking	34 (42)	8 (40)	0.316
<b>Baseline test scores</b>			
MMSE	28.1 ± 2.1 (27–30)	27.9 ± 2.6 (26–30)	0.276
TMT-a	57.9 ± 11.3 (40–80)	56.1 ± 16.1 (30–88)	0.581
TMT-b	126.1 ± 17.6 (100–161)	123.2 ± 20.1 (82–160)	0.542
RAVLT (delayed recall)	5.3 ± 1.1 (4–8)	5.9 ± 1.9 (2–9)	0.115
DST forward	5.2 ± 0.5 (4–6)	5.9 ± 1.3 (3–8)	0.088
DST backward	3.8 ± 0.6 (3–5)	3 ± 1.1 (1–4)	0.105
GPT dominant	102.1 ± 13.7 (78–131)	105.6 ± 18 (80–140)	0.372
GPT non-dominant	122.1 ± 15.3 (90–150)	122.7 ± 17.3 (99–164)	0.895

ASA, American Society of Anaesthesiologists; COPD, Chronic Obstructive Pulmonary Disease; CRF, Chronic Renal Failure; MMSE, Mini Mental State Examination; TMT, Trail Making Test; RAVLT, Rey Auditory Verbal Learning Test; DST, Digit Span Test; GPT, Grooved Pegboard Test.

years, respectively. The mean ages of the patients with and without POCD at postoperative 3 months were 70 ± 5 years and 61.2 ± 7.5 years, respectively. Although there was no significant age difference between patients with and without POCD at day 7 ( $p=0.062$ ), patients with POCD at 3 months were significantly older than those without POCD ( $p=0.030$ ). There was no significant difference in education level between patients with and without POCD. Tables 2 and 3 present the clinical characteristics of the non-POCD and POCD groups. At both 7 days and 3 months after surgery, the highest frequencies of impairment in neuropsychological tests were observed in TMT-a and TMT-b.

Serum S100B level was slightly increased after anesthesia induction, but the increase was not statistically significant compared to preoperative level ( $0.30 \pm 0.09$  vs.  $0.24 \pm 0.07$ , respectively,  $p=0.416$ ). However, serum S100B level was significantly elevated at postoperative 30 minutes compared to baseline ( $1.20 \pm 0.40$  vs.  $0.24 \pm 0.07$ , respectively,  $p=0.0001$ ). By 24 hours postoperatively, S100B level was decreased but remained significantly higher than baseline ( $0.43 \pm 0.18$  vs.  $0.24 \pm 0.07$ , respectively,  $p=0.005$ ). The relationship between S100B concentrations and neuropsychological test results after surgery are presented in Table 4. Elevated S100B concentrations at postoperative 30 minutes and 24 hours were associated with POCD. Patients displaying POCD at postoperative 7 days and 3 months had

significantly higher serum S100B levels at postoperative 30 minutes and 24 hours compared to patients without POCD (Figs. 1A and 1B).

Mean duration of anesthesia for all patients was  $327 \pm 62$  minutes. Duration of anesthesia was significantly longer in patients with POCD at postoperative 7 days and 3 months when compared with patients without POCD ( $p=0.012$  and  $p=0.001$ , respectively). Mean duration of Trendelenburg was  $236 \pm 56$  minutes overall and was also significantly longer in patients with POCD at postoperative 7 days and 3 months compared to patients without POCD ( $p=0.025$  and  $p=0.002$ , respectively) (Tables 2 and 3). Composite Z scores in tests performed on postoperative day 7 were significantly correlated with duration of Trendelenburg and anesthesia ( $p=0.0001$  for both) (Supplementary material Fig. S2A and S2B). A significant correlation was also detected between composite Z score in tests performed at postoperative 3 months and age ( $p=0.011$ ). However, composite Z score in tests performed at postoperative 3 months was not significantly associated with duration of Trendelenburg or anesthesia ( $p=0.055$  and  $p=0.063$ , respectively).

There were no significant differences in mean cerebral rSO<sub>2</sub> values after anesthesia induction, after Trendelenburg position, after end of the Trendelenburg position, or after end of surgery compared to baseline values.

**Table 2** Clinical features of patients with and without POCD on day 7 (values expressed as mean  $\pm$  standard deviation).

	POCD absent (n = 58)	POCD present (n = 24)	p-value
Age, years	60.6 $\pm$ 7.6	66 $\pm$ 7.2	0.062
Education, years	9.7 $\pm$ 3.3	10.7 $\pm$ 3.3	0.276
Duration of Trendelenburg, min	211 $\pm$ 36	296 $\pm$ 54	0.025 <sup>a</sup>
Duration of anesthesia, min	300 $\pm$ 37	394 $\pm$ 63	0.012 <sup>a</sup>
<i>S100B values</i>			
Baseline	0.24 $\pm$ 0.07	0.24 $\pm$ 0.07	0.967
After induction	0.30 $\pm$ 0.10	0.28 $\pm$ 0.09	0.473
Postoperative 30 min	1.01 $\pm$ 0.28	1.66 $\pm$ 0.26	0.0001 <sup>a</sup>
Postoperative 24 hours	0.36 $\pm$ 0.14	0.57 $\pm$ 0.19	0.001 <sup>a</sup>
<i>Baseline test scores</i>			
MMSE	27.4 $\pm$ 3.1 (27–30)	27.6 $\pm$ 2.2 (26–30)	0.496
TMT-a	58.9 $\pm$ 11.2	55.2 $\pm$ 11.3	0.246
TMT-b	128 $\pm$ 18.9	121.5 $\pm$ 13.5	0.195
RAVLT (delayed recall)	5.2 $\pm$ 1.1	5.5 $\pm$ 1.1	0.434
DST forward	5.2 $\pm$ 0.6	5.2 $\pm$ 0.5	0.763
DST backward	3.9 $\pm$ 0.5	3.7 $\pm$ 0.8	0.405
GPT dominant	104.3 $\pm$ 13.5	96.7 $\pm$ 12.9	0.046
GPT non-dominant	122.5 $\pm$ 15.1	121.2 $\pm$ 16.2	0.775
<i>Test scores on postoperative day 7</i>			
TMT-a	67.6 $\pm$ 10.4	106 $\pm$ 14.6	0.0001 <sup>a</sup>
TMT-b	133.8 $\pm$ 14.2	166.9 $\pm$ 17	0.0001 <sup>a</sup>
RAVLT	5.2 $\pm$ 0.9	4.5 $\pm$ 1.6	0.033 <sup>a</sup>
DST forward	4.3 $\pm$ 0.8	3.7 $\pm$ 1.2	0.059
DST backward	2.9 $\pm$ 0.7	2.6 $\pm$ 0.9	0.212
GPT dominant	108 $\pm$ 13	122.3 $\pm$ 27.4	0.007 <sup>a</sup>
GPT non-dominant	130.4 $\pm$ 17.4	155.6 $\pm$ 23.5	0.0001 <sup>a</sup>

POCD, Postoperative Cognitive Dysfunction; MMSE, Mini Mental State Examination; TMT, Trail Making Test; RAVLT, Rey Auditory Verbal Learning Test; DST, Digit Span Test; GPT, Grooved Pegboard Test.

<sup>a</sup>  $p < 0.05$ .

Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic value of serum S100B level for POCD. For POCD on day 7, the Areas Under the Curve (AUC) for baseline, after Trendelenburg, postoperative 30 minutes, and postoperative 24 hours were 0.495 ( $p = 0.951$ ), 0.410 ( $p = 0.271$ ), 0.965 ( $p = 0.0001$ ), and 0.802 ( $p = 0.0001$ ), respectively. A cut-off value of 1.35 for S100B at postoperative 30 minutes had sensitivity of 94.4% and specificity of 86.4% in the prediction of POCD on day 7. For S100B at postoperative 24 hours, a cut-off value of 0.47 had a sensitivity and specificity of 66.7% and 77.3%, respectively, for prediction of POCD on day 7 (Supplementary material Fig. S3A). For POCD at 3 months, AUC for baseline, after Trendelenburg, postoperative 30 minutes, and postoperative 24 hours were 0.414 ( $p = 0.463$ ), 0.339 ( $p = 0.168$ ), 0.916 ( $p = 0.0001$ ), and 0.877 ( $p = 0.001$ ), respectively. A cut-off value of 1.55 for S100B at postoperative 30 minutes had sensitivity and specificity of 85.7% and 87.3%, respectively, for POCD at 3 months, while a cut-off value of 0.47 for S100B at postoperative 24 hours had a sensitivity and specificity of 98.2% and 72.7%, respectively (Supplementary material Fig. S3B).

There were no complications such as brachial plexus injury or pneumothorax in any patients.

## Discussion

The present study showed that serum levels of S100B were significantly elevated at 30 minutes after RALRP and were decreased but still significantly higher than baseline at 24 hours after RALRP. The incidence of POCD was 29% at 7 days and 11% at 3 months after RALRP. Higher serum S100B levels at postoperative 30 minutes and 24 hours were associated with POCD at 7 days and 3 months after RALRP.

POCD is relatively common after major operations. Therefore, many studies have investigated short- and long-term POCD, including in patients undergoing major surgery.<sup>2,3,18–21</sup> The development of POCD after RALRP may be associated with a combination of several factors such as age, duration of steep Trendelenburg position, and duration of anesthesia.

Advanced age is defined as a risk factor for POCD. In non-cardiac surgeries, the incidence of POCD at postoperative 1 week was determined to be 26% in elderly patients, with 10% having persistent signs 3 months later.<sup>2</sup> In addition, it was shown that the incidence of POCD in elderly patients on the first day after minor surgery was higher than the reported incidence at 7 days after major surgery.<sup>22</sup> Another study reported the rate of POCD in patients aged 40–60 years

**Table 3** Clinical features of patients with and without POCD at 3 months (values expressed as mean  $\pm$  standard deviation).

	POCD absent (n = 73)	POCD present (n = 9)	p-value
Age, years	61.2 $\pm$ 7.5	70 $\pm$ 5	0.030 <sup>a</sup>
Education, years	9.8 $\pm$ 3.3	11.2 $\pm$ 2.8	0.303
Duration of Trendelenburg, min	227 $\pm$ 52	274 $\pm$ 37	0.002 <sup>a</sup>
Duration of anesthesia, min	317 $\pm$ 56	410 $\pm$ 52	0.001 <sup>a</sup>
<i>S100B values</i>			
Baseline	0.24 $\pm$ 0.07	0.22 $\pm$ 0.06	0.556
After induction	0.30 $\pm$ 0.10	0.25 $\pm$ 0.08	0.196
Postoperative 30 min	1.12 $\pm$ 0.34	1.80 $\pm$ 0.36	0.0001 <sup>a</sup>
Postoperative 24 h	0.40 $\pm$ 0.16	0.65 $\pm$ 0.17	0.001 <sup>a</sup>
<i>Baseline test scores</i>			
MMSE	26.9 $\pm$ 2.1 (27–30)	27.3 $\pm$ 3.1 (26–30)	0.541
TMT-a	57.7 $\pm$ 10.8	59.1 $\pm$ 15.4	0.761
TMT-b	126.6 $\pm$ 17.8	121.8 $\pm$ 17.1	0.502
RAVLT (delayed recall)	5.3 $\pm$ 1.1	5.4 $\pm$ 1.6	0.892
DST forward	5.2 $\pm$ 0.6	5.2 $\pm$ 0.4	0.837
DST backward	3.8 $\pm$ 0.6	4 $\pm$ 1	0.632
GPT dominant	103.2 $\pm$ 13.7	93.4 $\pm$ 11.1	0.075
GPT non-dominant	122.8 $\pm$ 15.2	116.7 $\pm$ 16.2	0.324
<i>Test scores at postoperative 3 months</i>			
TMT-a	66.3 $\pm$ 10.7	117.5 $\pm$ 13.2	0.0001 <sup>a</sup>
TMT-b	132.1 $\pm$ 18.8	167.2 $\pm$ 15	0.0001 <sup>a</sup>
RAVLT (delayed recall)	5.3 $\pm$ 1	3.5 $\pm$ 1.1	0.0001 <sup>a</sup>
DST forward	4.5 $\pm$ 0.8	2.7 $\pm$ 0.9	0.0001 <sup>a</sup>
DST backward	3.9 $\pm$ 0.7	3.8 $\pm$ 0.6	0.859
GPT dominant	107.4 $\pm$ 15	120.4 $\pm$ 31.7	0.070
GPT non-dominant	125.4 $\pm$ 17.5	150.2 $\pm$ 29.4	0.002 <sup>a</sup>

POCD, Postoperative Cognitive Dysfunction; MMSE, Mini Mental State Examination; TMT, Trail Making Test; RAVLT, Rey Auditory Verbal Learning Test; DST, Digit Span Test; GPT, Grooved Pegboard Test.

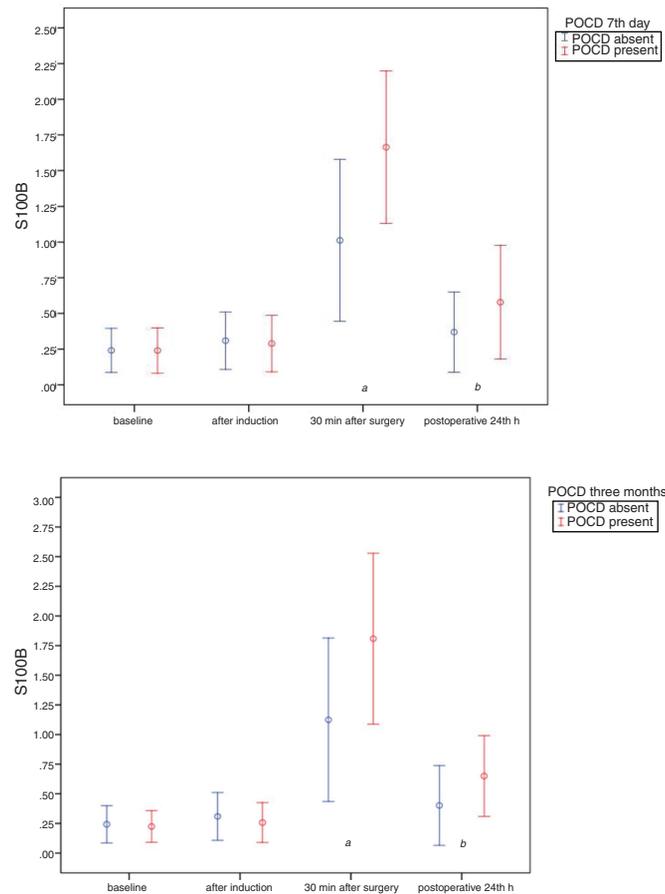
<sup>a</sup>  $p < 0.05$ .

**Table 4** The relationship between serum S100B concentrations at different time points and composite Z scores for postoperative cognitive dysfunction at 7 days and 3 months after surgery according to linear regression analysis.

	Coefficient (B)	Standard error	B	95% Confidence Interval	p-value
<i>Composite Z score on postoperative day 7</i>					
Baseline	4.573	6.538	0.106	−8.520–17.665	0.487
After Trendelenburg	−4.051	4.993	−0.121	−14.049–5.947	0.421
30 min after surgery	5.058	0.763	0.617	3.531–6.586	0.0001
24h after surgery	4.821	1.692	0.267	1.433–8.209	0.006
<i>Composite Z score at postoperative 3 months</i>					
Baseline	4.825	6.098	0.156	−7.386–17.035	0.432
After Trendelenburg	−2.723	4.656	−0.114	−12.047–6.60	0.561
Postoperative 30 min	1.631	0.711	0.279	0.206–3.055	0.026
Postoperative 24 h	4.773	1.578	0.37	1.613–7.932	0.004

as 19.2% at postoperative 1 week and 6.2% at 3 months.<sup>18</sup> Patients undergoing RALRP are generally elderly and are therefore at greater risk for POCD. In the current study, the mean age of the patients was 62.2  $\pm$  7.8 years. The incidence of POCD at postoperative day 7 was 29% and POCD persisted in 11% of the patients at 3 months after surgery. The mean age of the patients exhibiting POCD at 3 months was 70  $\pm$  5 years.

RALRP is one of the most commonly performed robotic surgeries and is performed with the patient in steep Trendelenburg position. The steep Trendelenburg position (45°) provides good surgical exposure during RALRP and is well tolerated by most patients. However, combined steep Trendelenburg position and pneumoperitoneum are known to increase ICP.<sup>23</sup> Increased ICP may decrease cerebral perfusion pressure and cerebral oxygenation.<sup>24,25</sup> Decreased



**Figure 1** A, Serum S100B level profiles according to presence or absence of POCD on postoperative (postop) day 7. Data are shown as mean  $\pm$  standard deviation. (a) Significant difference at postop 30 min between patients with and without POCD ( $p=0.0001$ ). (b) Significant difference at postop 24 h between patients with and without POCD ( $p=0.001$ ). B, Serum S100B level profiles according to presence or absence of POCD at postoperative (postop) 3 months. Data are shown as mean  $\pm$  standard deviation. (a) Significant difference at postop 30 min between patients with and without POCD ( $p=0.0001$ ). (b) Significant difference at postop 24 h between patients with and without POCD ( $p=0.001$ ).

cerebral oxygenation is a risk factor for POCD and is associated with delirium and prolonged hospitalization, particularly in elderly patients.<sup>26,27</sup> Pneumoperitoneum and 30° Trendelenburg position may not affect cerebral oxygenation within 2 hours because of physiological compensation mechanisms.<sup>28</sup> However, cerebrovascular autoregulation gradually changes with prolonged pneumoperitoneum in the 45° Trendelenburg position. Schramm et al. reported that cerebral autoregulation was impaired over time in the 45° Trendelenburg position, especially when it exceeded 170 minutes. They also pointed out that maintaining MAP within the normal range and minimizing the duration of Trendelenburg positioning might be useful to avoid neurological deterioration in patients placed in extreme Trendelenburg position for more than 3 hours.<sup>29</sup> In the current study, our finding of longer Trendelenburg time in patients with POCD supports the results obtained by Schramm. Kalmar et al. reported that regional cerebral oxygenation was well preserved in RALRP.<sup>30</sup> Consistent with this, although hemodynamic and pulmonary parameters and regional cerebral oxygenation remained within physiological limits in the present study, we observed a significant relationship

between duration of Trendelenburg and impairment in neurocognitive tests performed on postoperative day 7. However, this correlation was not detected for neurocognitive tests performed at postoperative 3 months.

The relationship between duration of anesthesia and POCD has been demonstrated in previous studies. Rohan et al. reported that the incidence of POCD in elderly patients was as high as 47% at 24 hours after minor surgeries not exceeding 30 minutes.<sup>22</sup> The high incidence of POCD in their study may be attributed to the fact that POCD was assessed 24 hours postoperatively. Patients who are still under the influence of anesthetic or analgesic drugs may have impaired cognitive performance. In order to rule out this possibility, it is recommended that the earliest test be conducted about 1 week after surgery, once centrally acting analgesics are no longer required and any active metabolites have been eliminated.<sup>31</sup> Canet et al. detected cognitive dysfunction in 9.8% of inpatients and 3.5% of outpatients at postoperative day 7. In that study, the median duration of anesthesia was 33 minutes and the authors reported that this was not a significant risk factor for POCD at 1 week.<sup>32</sup> In the ISPOCD1 study, the median duration of anesthesia was 190 minutes

and the incidence of POCD at 1 week was 18% when the duration was less than 2 hours and 27% when the duration was longer.<sup>2</sup> Similarly, Johnson et al. reported that the incidence of POCD was 29% if the duration of anesthesia was longer than 240 minutes.<sup>18</sup> In the present study, the mean duration of anesthesia in patients with POCD at 7 days after surgery was  $394 \pm 63$  minutes. Despite the relatively long duration of anesthesia in the current study compared to previous studies, the incidence of POCD at 7 days was 29%, which is consistent with the results of ISPOCD1 and Johnson et al.

It is known that S100B levels are elevated after cardiac surgery in particular<sup>33</sup> and correlate with POCD in some types of non-cardiac surgery.<sup>34</sup> A meta-analysis provided evidence that POCD is correlated with S100B concentrations.<sup>35</sup> Therefore, S100B seems to be a potential marker for POCD. Linstedt et al. reported that patients with POCD showed higher serum concentrations of S100B at postoperative 30 minutes compared to patients without POCD.<sup>36</sup> According to their study, elevation of S100B levels is short-lived, with peak serum concentrations occurring 30 minutes postoperatively and returning to basal level within 18 hours. Therefore, we measured serum S100B levels at postoperative 30 minutes and 24 hours. In addition to elevated S100B at postoperative 30 minutes in patients with POCD, we also found that S100B protein levels continued to be higher than baseline at 24 hours, which was not consistent with previous reports.

A major limitation to this study is the lack of long-term follow-up of cognitive function. We performed only early neurocognitive assessment.

## Conclusions

The present study suggests that the incidence of POCD in patients undergoing RALRP is 29% on postoperative day 7 and 11% at postoperative 3 months. Serum S100B increases after RALRP and this increase is associated with the development of POCD. Advanced age and duration of Trendelenburg position and anesthesia also contribute to the development of POCD. S100B levels along with multiple perioperative factors could be an effective predictor of POCD. Future studies with larger sample sizes and new biochemical markers will help to better understand the development of POCD.

## Authors' contributions

N.K.O. and A.S.K. conceived and performed the study, N.K.O., A.S.K. and U.A. analysed the data, and N.K.O., A.S.K., U.A., G.A. and M.S. approved the final manuscript.

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## Conflicts of interest

The authors declare no conflicts of interest.

## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.bjane.2020.06.016>.

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