EARLY AND LATE PREDICTORS OF POSTOPERATIVE NEUROCOGNITIVE DYSFUNCTION IN CARDIAC SURGERY

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Background and purpose – Postoperative cognitive dysfunction (POCD) is a multifactorial image characterized by insufficiency in features such as the ability to perform tasks requiring high brain functions. Cognitive dysfunction such as memory loss and decreased concentration, confusion, and delirium are common conditions in some patients in the early period after major surgical interventions such as cardiac surgery. POCD causes delays in postoperative recovery, long return-to-work times, and decreased quality of life. This study aims to demonstrate POCD in early and late stages in patients undergoing cardiac surgery through the Montreal Cognitive Assessment (MoCA) and the Mini Mental Test (MMT). In addition, we aim to determine predictive factors with these neurocognitive tests.
Methods – MMT and MoCA tests were applied to the patients included in the study before cardiac surgery, on the sixth postoperative day and third month. Neurocognitive dysfunction detected on the sixth postoperative day was accepted as an early period, its detection in the postoperative third month was accepted as a late period.
Results – 127 patients without neurocognitive dysfunction in the preoperative period were included in the study. For early neurocognitive impairment, age, mean platelet volume (MPV), New York Heart Association (NYHA) classification, x-clamp time, cardio-pulmonary bypass (CPB) time, postoperative intensive care and hospital stay duration, and an event of acute myocardial infarction (AMI) in the preoperative period were determined as predictive factors. In addition, in late-period of neurocognitive dysfunction age, MPV, NYHA classification, x-clamp duration, CPB time, postoperative intensive care and hospital stay duration were shown as predictors of neurocognitive dysfunction.

A POSZTOPERATÍV NEUROKOGNITÍV DISZFUNKCIÓ KORAI ÉS KÉSŐI PREDIKTORAI SZÍVSEBÉSZETI BEAVATKOZÁS UTÁN

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Háttér és cél – A posztoperatív kognitív diszfunkció (POCD) számos elemből összeálló állapot, amit a magasabb agyi funkciókat igénylő feladatok végrehajtásában jelentkező zavar jellemez. A nagy sebészeti beavatkozások, így például a szívsebészeti beavatkozások utáni korai időszakban gyakran jelenik meg memóriazavarral, csökkent koncentrációs készséggel, zavartsággal vagy delíriummal jellemezhető kognitív diszfunkció. A POCD következtében elhúzódik a posztoperatív gyógyulás, megnő a munkába való visszatéréshez szükséges időtartam és csökken a beteg életminősége. Vizsgálatunk célja az volt, hogy a Montreal Kognitív Felmérés (MoCA) és a Mini Mentális Teszt (MMT) segítségével felmérjük, milyen mértékben fordul elő POCD a szívsebészeti beavatkozások utáni korai és késői időszakban. Célunk volt továbbá annak megállapítása, hogy e neurokognitív tesztek a POCD milyen prediktív faktorait képesek kiszűrni.
Módszerek – A vizsgálatba bevont betegekkel a szívsebészeti beavatkozás előtt, a hatodik posztoperatív napon és a harmadik posztoperatív hónapban végeztük el a két tesztet. A hatodik posztoperatív napon detektált neurokognitív diszfunkciót korai, míg a harmadik posztoperatív hónapban detektált neurokognitív diszfunkciót késői POCD-nek számítottuk.
Eredmények – A vizsgálatba 127 olyan beteget vontunk be, akik a preoperatív periódusban nem rendelkeztek neurokognitív diszfunkcióval. A korai neurokognitív diszfunkciót a következő tényezők jelezték előre: életkor, átlagos vérlemezke-térfogat (MPV), New York Heart Association (NYHA-) osztályozás pontszáma, x-clamp-idő, cardiopulmonalis bypass (CPB) időtartama, a posztoperatív intenzív terápiás és kórházi ápolás időtartama, akut myocardialis infarktus (AMI) előfordulása a preoperatív periódusban.

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Conclusion – The results of our study support the literature findings showing that delirium is associated with a decline in cognitive functions three months after cardiac surgery. As a result, the lack of agreed diagnostic tests in the definition of POCD makes it difficult to standardize and interpret the research in this area. Therefore, a consensus to be reached in the diagnosis of POCD will ensure the use and correct interpretation of neurophysiological tests. In our study, advanced age and long hospital and intensive care stays were shown as predictive factors for both early and late neurocognitive dysfunctions. Furthermore, smoking was shown as a predictive factor only for late neurocognitive dysfunction.

Keywords: *cardiac surgery, neurocognitive disfunction, Montreal cognitive assesment, Mini Mental test*

A késői neurokognitív diszfunkciót a következő tényezők jelezték előre: életkor, MPV, NYHA-klasszifikáció, x-clamp-idő, CPB-időtartam, a posztoperatív intenzív terápiás és kórházi ápolás időtartama.
Következtetés – Eredményeink alátámasztják azt a szakirodalmi megállapítást, miszerint a delírium a szívsebészeti beavatkozások utáni harmadik hónapban a kognitív funkciók hanyatlásával jár együtt. Ebből az következik, hogy a POCD definiálásához használható standard diagnosztikai tesztek hiánya megnehezíti a kutatási eredmények interpretálását ezen a szakterületen. A neurofiziológiai teszteket csak akkor lehet majd megfelelő módon használni és interpretálni, ha kialakul a konszenzus a POCD diagnózisa kapcsán. Eredményeink szerint az előrehaladott életkor, valamint a hosszú posztoperatív intenzív terápiás és kórházi ápolási idő előre jelzi mind a korai, mind a késői neurokognitív diszfunkciót; a dohányzás csak a késői neurokognitív diszfunkció kockázati tényezője.

Kulcsszavak: *szívsebészet, neurokognitív diszfunkció, Montreal Kognitív Felmérés, Mini Mentális Teszt*

Postoperative cognitive dysfunction (POCD) is a multifactorial image characterized by insufficiency in features such as the ability to perform tasks requiring high brain functions. Symptoms and severity vary in each patient. Cognitive changes are usually temporary, but in some cases, they may last for weeks after anesthesia, or even be permanent and may be a precursor to further disorders. Cognitive function is defined as a person's functions to use perception, memory, and information[1]. Cognitive dysfunction such as memory loss and decreased concentration, confusion, and delirium are common conditions in some patients in the early period after major surgical interventions such as cardiac surgery[2]. Although the etiology of postoperative cognitive dysfunction is not fully known, it is thought to be multifactorial. Popular opinions today are that the answer to POCD formation is a systemic inflammatory response triggered by the joint effect of stress response during surgery, the type of surgery and anesthesia[3]. Although developments in surgical and anesthesia techniques in recent years have significantly decreased the frequency of all kinds of serious complications after major surgery, POCD is still frequently encountered, especially in elderly patients. Although different rates are reported depending on the type and length of anesthesia and surgery, evaluation methods, and definitions, a frequency varying between 20-80% is reported[4]. POCD has been shown to have negative effects on clinical results by prospective clinical studies[5, 6]. POCD causes delays in postoperative recovery, long return-to-work times, and decreased quality of life[7].

Since a weak correlation has been shown between self-definition of cognitive symptoms and objective tests, pre- and post-operative neuropsychological tests are used for the diagnosis of POCD[8]. The Montreal Cognitive Assessment (MoCA) and the Mini Mental Test (MMT) are commonly used tests in many centers in the diagnosis of cognitive dysfunction. MMT is a bedside test that can be applied by healthcare professionals in a short time. MoCA[9], which has higher sensitivity and specificity compared to MMT in the evaluation of neurocognitive dysfunctions, has excellent sensitivity to define mild cognitive impairment (90%) and very good specificity (87%), and it also has good test-retest reliability ($r=0.92$, $p=0.001$)[10]. MoCA is used to differentiate cognitive weakness in vascular cognitive dysfunctions, vascular dementia, and cardiovascular diseases[11]. A test that can be defined as the "gold standard" for postoperative cognitive dysfunction has not yet been developed. MMT, which is one of the neurological examination and neurophysiological tests in a clinic, is frequently preferred for its ease of application. However, there are no studies showing that the more sensitive MoCA test is used in the postoperative period in PCOD patients.

In this study, we aim to investigate the predictive factors of POCD and their effect on postoperative clinical results and to contribute to the literature on the management of the disease.

Materials and methods

The study was approved by the Adiyaman University ethics committee with the approval number of 2020/6-39. All patients who underwent cardiac surgery in our hospital over a period of 3 months were included in the study after obtaining their written consent. Patients with preoperative neurocognitive dysfunction (MoCA<21 / MMT <26), education level below secondary education, a neurological and psychiatric disease, an alcohol and substance addiction, a chronic renal failure, not providing consent to the study, with clinical conditions that may lead to cerebral ischemia during the study (cerebral embolism, long-term hypotension, cardiac arrest, or respiratory arrest), and patients with cerebral hemorrhage were not included in the study.

Anesthesia premedication was provided in all patients by administering Diazepam 5 mg per os the night before the operation, and Morphine sulfate 10 mg im. 30 minutes before the operation. After the patient was taken to the operating room they were monitored, and ECG electrodes, venous tracts and a radial artery catheter for full arterial monitoring were placed, and the anesthesia induction was performed with fentanyl 30-50 μg/kg. Succinyl Choline 1 mg/kg was used, and pancuronium 0.1 mg/kg was used as a muscle relaxant. 3 μg/kg/min fentanyl infusion and isoflurane inhalation were used for the maintenance treatment. Intubated patients were ventilated with 100% O_2. A Foley catheter was used to monitor urine output during the operation. Under general anesthesia, median sternotomy was performed, left internal mammarian artery and saphenous vein grafts were used. A centrifugal bypass pump and a membrane oxygenator were used and moderate hypothermia was applied. All cases were heparinized and the activated clotting time (ACT) was kept above 400 seconds. The pump flow rate was adjusted to 2.4 L/min/m^2 according to the body surface area of the patients. Cold blood cardioplegia was applied. Patients who were taken to the intensive care unit were extubated when appropriate alertness was observed and there was no problem in blood gas and chest tube drainage. Patients who were followed up in the intensive care unit on the first and second days after the operation were taken to the ward on the second postoperative day if there was no additional problem. Patients who did not have any problem during follow-up in the ward were discharged on the sixth postoperative day.

MMT and MoCA were applied to all patients on the morning of the operation, after the operation, on the sixth postoperative day and on the third postoperative month, which provides the data for this study. The tests used in the study were determined by a neurologist and scored by the same neurologist (Y.A). In the questionnaires used in the study, orientation, recording memory, attention, calculating, language, concentration, memory, executive function, abstract thinking, and orientation tests were used. A score of 21 for the MoCA test and under 26 for the MMT was considered to be a neurocognitive dysfunction. Care was taken to ensure that the test conditions applied were the same for each patient. The tests were administered at the same time of day, in the same room, and by the same person each time. Detection of a neurocognitive dysfunction on the sixth postoperative day was defined as an early neurocognitive dysfunction, and the continuation of the condition in the third postoperative month as a late neurocognitive dysfunction.

Preoperative analysis and examination results were compared with the preoperative data of the patients, including age, gender, body mass index, NYHA functional class, smoking status, comorbid diseases (diabetes mellitus, hypertension, and chronic obstructive pulmonary disease). The x-clamp and cardiopulmonary bypass times from the operative data of the patients, the duration of stay in the intensive care unit, hospital stay, mechanical ventilation time from the postoperative parameters, and the postoperative blood tests and ejection fraction results were compared.

STATISTICAL ANALYSIS

The SPSS 11.5 program was used for data analysis. As descriptors, mean±standard deviation and median (minimum-maximum) were used for the quantitative variables and the number of patients (percentage) for the qualitative variables. Whether there is a difference between the categories of the qualitative variable with two categories in terms of quantitative variables were examined using the Student's t-test if normal distribution assumptions were provided, and the Mann-Whitney U test if not. When the relationship between the two qualitative variables was analyzed, the Chi-square test was used. Univariate and Multivariate Logistic Regression analyzes were used to determine the risk factors affecting neurocognitive dysfunction. The statistical significance level was taken as 0.05.

Table 1. *Demographic Data for Early Neurocognitive Disorder-1*

Variables	Early neurocognitive dysfunction				
	No		Yes		
	Mean±S.D.	Median (Min.-Max.)	Mean±S.D.	Median (Min.-Max.)	p-value
Age	54.55±8.81	55.50 (34.00-70.00)	66.16±7.39	66.00 (53.00-83.00)	*<0.001*[a]
BMI	27.30±3.82	27.35 (19.10-37.30)	27.94±4.50	27.50 (18.60-40.00)	0.390[a]
AST	24.74±11.13	22.00 (12.00-64.00)	26.36±11.92	24.00 (10.00-64.00)	0.434[b]
ALT	24.29±11.96	21.50 (10.00-70.00)	26.20±17.11	22.00 (7.00-111.00)	0.799[b]
Albumin	4.10±0.27	4.10 (3.60-4.59)	4.03±0.43	4.00 (2.80-4.82)	0.493[b]
Urea	40.81±12.74	39.00 (21.00-71.00)	38.07±14.98	37.00 (20.00-123.00)	0.202[b]
Creatine	0.90±0.19	0.92 (0.44-1.49)	0.89±0.17	0.87 (0.60-1.60)	0.176[b]
MPV	8.13±0.94	8.20 (6.29-10.60)	8.93±1.16	8.78 (6.36-11.20)	*<0.001*[a]
Hemoglobin	14.36±1.62	14.35 (9.80-16.90)	13.88±1.75	13.70 (9.60-18.00)	0.076[b]
NYHA	1.84±0.64	2.00 (1.00-3.00)	2.26±0.66	2.00 (1.00-4.00)	*0.001*[b]
Ejection fraction	50.67±8.65	53.50 (30.00-63.00)	49.71±7.62	50.00 (30.00-65.00)	0.234[b]
MoCA on the preoperative-postoperative 6th day	2.38±1.45	2.00 (0.00-7.00)	8.49±4.85	8.00 (2.00-19.00)	*<0.001*[b]
MMT on the preoperative-postoperative 6th day	2.29±1.58	2.00 (0.00-6.00)	7.16±3.22	7.00 (1.00-17.00)	*<0.001*[b]

SD: standard deviation, Min.: minimum, Max.: maximum, a: Student-t test, b: Mann-Whitney U test, BMI: body mass index, AST: aspartate amino transferase, ALT: alanine amino transferase, MPV: mean platelet volume, NYHA: New York Heart Association, MoCA: Montreal Cognitive Assessment, MMT: Mini Mental test

Results

127 patients without preoperative neurocognitive dysfunction were included in the study. While a neurocognitive dysfunction was observed in 69 (54.3%) patients in the early period, it was observed that such a condition continued in the late period in 25 (19.6%) patients. When the demographic characteristics of patients with early neurocognitive dysfunction were examined, age, mean platelet volume (MPV), New York Heart Association (NYHA) classification and acute myocardial infarction (AMI) were found to be statistically more significant in the group with a neurocognitive dysfunction ($p<0.05$) (**Tables 1** and **2**). The x-clamp time, cardio-pulmonary bypass (CPB) time, duration of stay in the intensive care unit and in the hospital were found to be statistically more significant in patients with an early neurocognitive dysfunction ($p<0.001$) **(Table 3)**. Compared to preoperative values, the MoCA and MMT scores were found to be statistically less significant on the 6th postoperative day **(Table 1)**.

Age, MPV, NYHA classification, x-clamp time, CPB time, postoperative length of intensive care unit and inpatient hospital stays, and occurrence of AMI in the preoperative period, were found to be significant as a result of the analysis in **Tables 1, 2** and **3**. Factors thought to have an effect on early neurocognitive dysfunction were included in the regression analysis **(Table 4)**. Considering the results of the univariate logistic regression analysis in Table 4, all variables were found to be significant risk factors and were included in the multivariate logistic regression analysis. According to the multivariate logistic regression results, the variables of age, MPV, postoperative intensive care duration (days), hospital stay (days) and preoperative AMI all combined were found to be significant in the model. The risk of early neurocognitive dysfunction increased by 1.235 times for every single unit of increase in age factor, by 2.615 times for each single unit of increase in MPV, by 1.095 times per unit of increase in postoperative intensive care duration (day) and by a multiple of 2.072 for every single unit of increase in hospital stay (day). AMI, on the other hand, increases the risk of early neurocognitive dysfunction by 5.733 times **(Table 4)**.

When the demographic characteristics of the patients with late-stage neurocognitive impairment were examined, age, MPV and high NYHA classi-

Table 2. *Demographic Data for Early Neurocognitive Disorder-2*

Variables		Early neurocognitive dysfunction				
		No		Yes		
		N	%	N	%	p-value
Gender	Male	44	75.9	50	72.5	0.664
	Female	14	24.1	19	27.5	
Smoking Status	No	18	31.0	22	31.9	0.918
	Yes	40	69.0	47	68.1	
DM	No	24	41.4	28	40.6	0.927
	Yes	34	58.6	41	59.4	
COPD	No	48	82.8	49	71.0	0.121
	Yes	10	17.2	20	29.0	
TFT Disorder	No	48	82.8	58	84.1	0.844
	Yes	10	17.2	11	15.9	
HT	No	26	44.8	28	40.6	0.630
	Yes	32	55.2	41	59.4	
AMI	No	42	72.4	36	52.2	*0.020*
	Yes	16	27.6	33	47.8	

DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, TFT: thyroid function test, HT: hypertension, AMI: acute myocardial infarction

Table 3. *Operative and postoperative data for early neurocognitive impairment*

Variables	Early neurocognitive dysfunction				
	No		Yes		
	Mean±S.D.	Median (Min.-Max.)	Mean±S.D.	Median (Min.-Max.)	p-value
X-Clamp time	64.76±12.91	64.50 (35.00-96.00)	78.07±17.60	76.00 (48.00-143.00)	*<0.001*[b]
CPB time	87.64±13.36	89.50 (60.00-110.00)	114.39±24.89	110.00 (75.00-194.00)	*<0.001*[b]
Postoperative intensive care time (days)	31.14±12.78	26.00 (23.00-72.00)	63.70±37.35	48.00 (21.00-268.00)	*<0.001*[b]
Hospital stay (days)	5.78±1.43	5.00 (4.00-12.00)	9.12±5.76	8.00 (6.00-48.00)	*<0.001*[b]
Postoperative Ventilation Time (hours)	8.73±2.46	8.00 (5.00-18.00)	11.81±14.73	8.00 (4.00-124.00)	0.554[b]

CPB: cardiopulmonary bypass

Table 4. *Univariate logistic regression analysis results for early neurocognitive dysfunction*

Variables (Reference)	β	S.E.	p-value	OR	95% CI for OR	
					Lower limit	Upper limit
Age	0.183	0.034	*<0.001*	1.201	1.124	1.283
Mean Platelet Volume	0.705	0.188	*<0.001*	2.024	1.400	2.925
NYHA	0.989	0.300	*0.001*	2.688	1.494	4.836
X-Clamp time	0.066	0.016	*<0.001*	1.068	1.035	1.102
CPB time	0.093	0.018	*<0.001*	1.097	1.059	1.138
Postoperative intensive care time (days)	0.089	0.016	*<0.001*	1.093	1.059	1.129
Hospital stay (days)	1.192	0.219	*<0.001*	3.295	2.144	5.063
AMI	0.878	0.380	*0.021*	2.406	1.143	5.067

β: Beta coefficient, S.E.: standard error of mean, OR: odds ratio, CI.: confidence interval, NYHA: New York Heart Association, CPB: cardiopulmonary bypass, AMI: acute myocardial infarction

Table 5. *Demographic Data for Late Neurocognitive Dysfunction-1*

Variables	Late neurocognitive dysfunction				
	No		Yes		
	Mean±S.D.	Median (Min.-Max.)	Mean±S.D.	Median (Min.-Max.)	p-value
Age	59.29±9.66	60.00 (34.00-81.00)	67.24±8.40	66.00 (54.00-83.00)	*<0.001*[a]
BMI	27.74±4.23	27.70 (18.60-37.80)	27.30±4.14	27.00 (20.20-40.00)	0.644[a]
AST	26.01±11.47	24.00 (12.00-64.00)	24.04±11.97	24.00 (10.00-64.00)	0.345[b]
ALT	25.90±15.89	22.00 (8.00-111.00)	23.00±10.23	21.00 (7.00-48.00)	0.748[b]
Albumin	4.06±0.35	4.10 (2.80-4.82)	4.09±0.44	4.10 (2.90-4.70)	0.438[b]
Urea	39.31±14.29	37.50 (20.00-123.00)	39.36±13.12	38.00 (21.00-87.00)	0.713[b]
Creatine	0.90±0.17	0.90 (0.44-1.49)	0.87±0.22	0.81 (0.60-1.60)	0.178[b]
MPV	8.46±1.08	8.50 (6.29-11.20)	9.01±1.28	9.15 (6.77-11.20)	*0.028*[a]
Hemoglobin	14.12±1.69	14.20 (9.60-16.90)	14.03±1.81	13.64 (10.50-18.00)	0.544[b]
NYHA	2.01±0.71	2.00 (1.00-4.00)	2.32±0.48	2.00 (2.00-3.00)	*0.037*[b]
Ejection Fraction	50.43±7.70	50.00 (30.00-65.00)	49.00±9.57	50.00 (30.00-65.00)	0.453[b]
MoCA on preoperative-postoperative 3rd month	2.05±1.86	1.00 (0.00-8.00)	9.08±5.62	7.00 (2.00-19.00)	*<0.001*[b]
MMT on preoperative-postoperative 3rd month	2.20±1.71	2.00 (0.00-9.00)	6.64±3.49	6.00 (1.00-16.00)	*<0.001*[b]

SD: standard deviation, Min.: minimum, Max.: maximum, a: Student-t test, b: Mann-Whitney U test, BMI: body mass index, MPV: mean platelet volume, AST: aspartate amino transferase, ALT: alanine amino transferase, NYHA: New York Heart Association, MoCA: Montreal Cognitive Assessment, MMT: Mini Mental test

Table 6. *Demographic Data for Late Neurocognitive Dysfunction-2*

Variables		Late neurocognitive dysfunction				
		No		Yes		
		N	%	N	%	p-value
Gender	Male	77	75.5	17	68.0	0.444
	Female	25	24.5	8	32.0	
Smoking Status	No	27	26.5	13	52.0	*0.014*
	Yes	75	73.5	12	48.0	
DM	No	42	41.2	10	40.0	0.915
	Yes	60	58.8	15	60.0	
COPD	No	79	77.5	18	72.0	0.565
	Yes	23	22.5	7	28.0	
TFT Disorder	No	84	82.4	22	88.0	0.496
	Yes	18	17.6	3	12.0	
HT	No	47	46.1	7	28.0	0.101
	Yes	55	53.9	18	72.0	
AMI	No	63	61.8	15	60.0	0.871
	Yes	39	38.2	10	40.0	

DM: diabetes mellitus, COPD: chronic obstructive pulmonary disease, TFT: thyroid function test, HT: hypertension, AMI: acute myocardial infarction

fication variables were found to be statistically more significant in the group with a neurocognitive dysfunction (p <0.05) **(Table 5)**. There was no difference between the groups in terms of having AMI (p=0.871). Smoking was found to be statistically more significant in the group with a late neurocognitive dysfunction (p=0.014) **(Table 6)**. X-clamp time, CPB time, ICU and hospital stay times were statistically significantly higher in patients with an early neurocognitive dysfunction (p<0.001) **(Table 7)**. When compared with their preoperative values, MoCA and MMT scores were found to be statisti-

Table 7. *Operative and Postoperative Data for Late Neurocognitive Dysfunction*

Variables	Late neurocognitive dysfunction				
	No		Yes		
	Mean±S.D.	Median (Min.-Max.)	Mean±S.D.	Median (Min.-Max.)	p-value
X-Clamp time	67.62±12.54	68.00 (35.00-96.00)	89.84±20.77	82.00 (60.00-143.00)	*<0.001*[b]
CPB time	92.96±14.08	95.00 (60.00-129.00)	139.76±21.26	137.00 (113.00-194.00)	*<0.001*[a]
Postoperative intensive care time (days)	41.06±31.18	28.00 (21.00-268.00)	80.52±18.39	72.00 (48.00-120.00)	*<0.001*[b]
Hospital stay (days)	6.90±2.60	6.00 (4.00-24.00)	10.40±8.65	8.00 (6.00-48.00)	*<0.001*[b]
Postoperative Ventilation Time (hours)	10.37±12.06	8.00 (4.00-124.00)	10.56±5.44	9.00 (4.00-23.00)	0.341[b]

CPB: cardiopulmonary bypass

Table 8. *Univariate logistic regression analysis results for late neurocognitive dysfunction*

Variables (Reference)	β	S.E.	p-value	OR	95% CI for OR	
					Lower limit	Upper limit
Age	0.097	0.029	*0.001*	1.102	1.042	1.165
Mean Platelet Volume	0.433	0.201	*0.032*	1.542	1.039	2.287
NYHA	0.693	0.344	*0.044*	2.000	1.019	3.928
X-Clamp time	0.102	0.024	*<0.001*	1.108	1.057	1.160
CPB Time	0.289	0.076	*<0.001*	1.336	1.151	1.550
Postoperative intensive care time (days)	0.043	0.010	*<0.001*	1.044	1.024	1.066
Hospital stay (days)	0.183	0.074	*0.013*	1.200	1.039	1.386

β: Beta coefficient, S.E.: standard error of mean, OR: odds ratio, CI.: confidence interval, NYHA: New York Association, CPB: cardiopulmonary bypass

cally significantly lower in the postoperative 3rd month **(Table 5)**.

Age, MPV, NYHA classification, x-clamp time, CPB time, and postoperative intensive care and hospital stay times, which were found to be significant as a result of the analyzes in **Tables 5**, **6** and **7** and also thought to affect late neurocognitive dysfunction, were included in the univariate logistic regression analysis **(Table 8)**. Considering the results of the univariate logistic regression analysis in **Table 8**, all variables were found to be significant risk factors and were included in the multivariate logistic regression analysis. According to the multivariate logistic regression results, x-clamp times and postoperative intensive care times (days) both were found to be significant together in the model. A one unit increase in the x-clamp time was found to increase the risk of late-stage neurocognitive dysfunction by 1.112-fold and a one unit increase in the postoperative intensive care time (day), by 1.032-fold **(Table 8)**.

Discussion

In this study, POCD was shown with low MoCA values in the early period affecting 54.3% of patients, and in the late period 19.6% of patients. POCD in cardiac surgery has been the subject of research and discussion for many years. In a study conducted on patients who underwent coronary artery surgery, it was shown that 40-80% of the patients had a decrease in mental abilities such as concentration, attention, and memory[12]. POCD is the most common neurological disorder after cardiac surgery. It is a problem that affects not only patients, but also their relatives and may cause additional costs in the health systems in both the long and short-terms[13]. Many factors in the preoperative, operative and postoperative phases can lead to POCD. Although the incidence of POCD after coronary artery bypass graft operation is found to be high in the early period, the majority of patients can return to their preoperative basal neurocogni-

tive values[14]. Therefore, POCD can be said to be time-dependent. Most dysfunctions are observed at the time of discharge. While neurocognitive dysfunction is observed at a rate of 50-80% at the time of discharge, it is observed with a rate of 20-50% in the 6th week and 10-30% in the 6th month[15]. *Newman* et al. observed a decrease in cognitive function in 53% of the patients at the time of discharge, in 36% after 6 months and in 42% after 5 years, and thought that the most important predictor of late-stage cognitive dysfunction was early cognitive dysfunction[12]. *Johnson* et al. in a study involving patients aged 68 and over, found that 26% of the patients had PCOD in the first postoperative week after non-cardiac surgery, while only 10% of patients had a cognitive dysfunction in the third postoperative month[16]. Similar to previous studies, it was observed in our study that the neurocognitive disorders in the early period did not persist in the third postoperative month in most patients. While the incidence of neurocognitive dysfunction was 54.3% of patients in the early postoperative period, it was found that the situation continued in 19.6% of the patients in the late period. This may be due to the unstable performance of the patients in the early period. It may also be due to the use of MMT as a neuropsychological test battery in other studies and the use of the more-sensitive MoCA in our study.

Cognitive dysfunctions are more common in the elderly. The increase in the mean age in the patient group that will undergo cardiac surgery has brought concerns about POCD. Cognitive functions are very important in this patient group in order to overcome post-operative physical difficulties. Therefore, POCD formation can lead to a failure in the postoperative period. The associated increased delirium risk also affects the postoperative results[17]. Advanced age is one of the risk factors for the occurrence of POCD. Brain blood flow and brain mass decrease in elderly patients, neuronal loss and changes in neurotransmitter concentrations increase the possibility of postoperative cognitive dysfunction[3]. In our study, advanced age was observed as a predictive factor in univariate analysis for early and late neurocognitive dysfunction. In the multivariate analyzes, it was shown to be an independent predictor of early neurocognitive dysfunction. In the study conducted by *Selnes* et al., the effect of age on cognitive dysfunctions was attributed to the higher prevalence of other risk factors, such as diabetes mellitus and kidney failure in the elderly population[15]. However, the fact that there was no difference in the incidence of comorbidities between the groups in our study has shown that the age factor alone is a predictor of neurocognitive dysfunction. *Sauër* et al. showed that advanced age prolonged the duration of POCD[18]. The fact that age was found to be one of the predictors of late-stage neurocognitive dysfunction in our study supports the findings of this study. In a study in which postoperative delirium was evaluated with the Confusion Assessment Method (CAM), postoperative delirium was independently associated with cognitive decline one month after surgery[19]. In our study, MoCA and MMT scores were found to be statistically significantly lower at the third postoperative month compared to the preoperative values.

In our study, chronic smoking was found to be a predictor of late-stage neurocognitive dysfunction in the univariate analyzes. The effect of smoking on neurocognitive performance is divided into two as acute and chronic. It increases cognitive performance through nicotine in the acute effect, while in chronic use it is associated with poor cognitive function due to the vascular damage it causes[20]. There are studies indicating that factors predisposing to vascular diseases such as hypertension, hypercholesterolemia, and smoking cause cognitive dysfunction[21]. These factors are also associated with postoperative delirium[22,23]. *Pérez Belmonte* et al. have shown that smoking is one of the POCD factors[24]. *Heffernan* et al. have associated chronic smoking with short and long-term memory problems[25]. However, in a study by *Djaiani* et al., age, cognitive function, years of education, and impaired left ventricular function were shown as predictive factors of neurocognitive decline in the 6th week after CABG, while the preventive or causative effect of smoking could not be demonstrated[26]. The fact that patients had a preoperative AMI triggers both an acute inflammation and prolongs hospital stay. In our study, having preoperative AMI and preoperative MPV were shown as independent predictors of early POCD. While MPV was also observed as a predictor of late POCD in univariate analyzes, the effect of AMI was not observed in chronic POCD. MPV is one of the indicators of the inflammatory process and shows the platelet size. In our study, the inflammatory process caused by AMI may have triggered the early period neurocognitive dysfunction and the increase in MPV. By *Beeri* et al. inflammation was shown as a common factor in coronary artery disease and cognitive disorders[27]. The decrease in inflammation due to AMI over time may explain that it is not a factor in late neurocognitive dysfunction.

NYHA classes are among the indicators of cardiac symptoms, cardiac status and functional capacity[28]. There are studies in the literature that associate low functional capacity and high NYHA

classes with neurocognitive dysfunction[29]. In our study, low functional capacity was detected as one of the indicators of early and late neurocognitive dysfunction in univariate analyzes. This can be attributed to the long recovery times and the long time to return to normal activities of patients with low functional capacity.

In our study, x-clamp and CPB times were shown as predictors of early and late neurocognitive dysfunction in univariate analyzes. The cases that require a long x-clamp time also lead to an increase in CPB times. *Kilo* et al., in their study on CABG patients, also showed CPB as the only predictor of neurocognitive dysfunction after CABG[30]. Again, *Xu* et al. and *Boodhwani* et al. demonstrated cardiopulmonary bypass times as predictors of POCD[31, 32]. The action mechanisms of cardiopulmonary bypass and x-clamp times are not yet fully understood. As it is known, body blood flow in the x-clamp process is provided by a completely artificial system. Debates continue about how optimal cerebral perfusion should be in this process. It is known that low cerebral perfusion and high cerebral perfusion under an X-clamp affects cognitive functions severely[33]. Inappropriate cerebral perfusion pressure combined with prolonged CPB and x-clamp times may have caused POCD. Moreover, particle or gas micro-embolisms and inflammatory mediators that occur as a result of blood contact with foreign surfaces may be the cause of this situation[34].

In our study, long hospital and intensive care stays were shown as predictors of both early and late neurocognitive dysfunctions. Similarly in the literature, it was found that in case of elective patients with a preoperative MoCA score lower than 26 who underwent open-heart surgery, the cost of mechanical ventilation, the duration of stay in the intensive care unit and in hospital were significantly increased, but postoperative cognitive involvement was not mentioned[35]. In addition, *Wilson* et al. and *Steinmetz* et al. showed in their large-scale studies that long hospital and intensive care stays lead to neurocognitive dysfunctions[36, 37]. The most important consequence of postoperative cognitive dysfunction is that patients lose their functional independence. In the postoperative period, this situation causes prolongation of the intensive care stays. According to our study, long intensive care stays may be a result of both postoperative dysfunction and a cause of early and late neurocognitive dysfunction.

The results of our study support the literature findings showing that delirium is associated with a decline in cognitive functions three months after cardiac surgery. As a result, the lack of agreed diagnostic tests in the definition of POCD makes it difficult to standardize and interpret the research in this area. Therefore, a consensus to be reached in the diagnosis of POCD will ensure the use and correct interpretation of neurophysiological tests. Large-scale studies are needed to precisely determine how MoCA, a new generation test, is affected by cardiopulmonary bypass and anesthetics in patients undergoing CABG surgery. Thus, it will be possible to determine whether MoCA will be included in the routine postoperative evaluation.

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