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**DIAGNOSTIC CRITERIA FOR POST-OPERATIVE COGNITIVE
DYSFUNCTION: LITERATURE REVIEW**

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Introduction

In 1955, for the first time, Betford described POCD in elderly persons [2] and this way, he started a new direction for research.

POCD is defined as a decline of cognitive functions following surgery at several weeks or months distance [3]. Incidence of POCD in heart surgery varies between 30% and 80% during the first postoperative week, being 60% in the following several months [4, 5]. In major, non-cardiac surgery, POCD has an incidence of 26% at one week distance after the surgery, being 10% at 3 months after the surgery [6].

Patients that showed signs of POCD at discharge, had higher mortality risks in the first 3 months of the postoperative period. According to Steinmetz *et al*, patients that showed cognitive impairment during 3 postoperative months as well, had higher chances to die in the first postoperative year (2009) [7].

The mechanism of POCD is not yet known, but neuro-inflammation is blamed to be one of the causes [8]. There is a variety of other factors that may contribute to the development of POCD and can't be ignored: age, educational level, strokes [6], major surgery or history of multiple surgeries [9], genetic factors (apoprotein E) etc [10].

POCD was evaluated using batteries of neuro-psychological tests that cover several areas of cognitive functions such as reading, memorizing, orientation etc. So, the multitude of tests used by different researches raise a lot of questions: is it possible to create a single test that would reflect all areas of cognitive function? Which would be the ideal combination between these tests in order to establish POCD?

Unification of these questionnaires and an ideal template has not been created yet. Thus, the proposed questionnaires need to be validated as a screening method of POCD.

Material and methods

In order to reach the aim of this study, relevant articles were searched for in PubMed data base, published in the last 15 years. The following key-words were used: postoperative cognitive dysfunction diagnostic criteria, assessment, evaluation. Only articles written in English were selected. Exclusion criteria were: article not available in full-text, lots of patients less than 100, synthesis articles, methanalysis, restrospective research aticles, articles based on delirium, research that enrolled patient that underwent neurosurgery, Parkinson or Alzheimer, research among children, animal studies

Results

A number of 296 articles were identified and sorted according to inclusion criteria (Fig . 1). Ten articles were subject of final analysis (Tab. 1).

Results observed during final analysis:

- Number of patients enrolled in the study was ranging from 100 to 997 patients.
- The following diagnostic tools were identified: MMSE (Mini Mental State Examination), TMT (Trail Making Test or Korean Trail Making Test), RAVLT (Rey's Auditorial Verbal Learning Test), RAVLT-LT (Rey's Auditorial Verbal Learning Test Long Term Memory), GP / PBT (Grooved pegboard, preferred hand, non dominant), STROOP (Stroop color word interference test), DST (Digit Span Test), DSST (Digit Symbol Substitution Test), VFT (Verbal Fluency Test), VVL (Visual Verbal Leaning), ECO (Examen Cognitif par Ordinateur), DECO (Deterioration Cognitive Observee).
- As diagnostic tools for POCD a number of test from 2 to 10 tests were used per research. In a total number of 10 articles, 24 questionnaires were used. Thus, 1

questionnaire is present in 6 different articles, 3 questionnaires are present in 5 articles, 1 questionnaire is used in 4 articles, 6 questionnaires is stated in 3 articles, 4 questionnaires is present in 2 articles and 9 questionnaires were stated 1 time each.

- Most of the studies were focused on cardiac surgery, being used in 6 out of 10 articles. Also orthopedic and urological surgery and invasive procedures such as coronarography were stated as well.
- According to the analyzed studies, the incidence of POCD ranges between 3.1% and 52%.

Table 1.

Author [reference] (type of study)	Number of patients	Diagnostic tool	Type of surgery	Diagnostic criteria for POCD	Results
Lene Krenk <i>et al.</i> ; 2014 [11], (prospective, multicentric)	225 patients included in the first step	1. VVL 2. Concept Shifting Test 3. STROOP 4. Letter Digit Coding Task	Hip and knee arthroplasty	Individual Z score > 1.96 Mixed Z score > 1.96	1. Early POCD in 20 patients out of 220 included in the first testing after the surgery (9.1%; 95% CI, 5.4%-13.1%). 2. Late POCD at 3 months: 16 out of 199 cases (8.0%; 95% CI, 4.5%-12.0%).

Seong Wook Hong <i>et al.</i> , 2008 [12], (prospective study)	100 patients included in statistical analysis	<ol style="list-style-type: none"> 1. MMSE 2. TMT 3. GP 	Cardiac valve replacement	POCD was found at least in 1 out of 3 tests	POCD found in 23% cases
Meybohm P. <i>et al.</i> ; 2013 [13] (prospective, randomized, double-blind)	180 patients	<ol style="list-style-type: none"> 1. RAVLT 2. RAVLT LT 3. PBT dominant 4. PBT non dominant 5. STROOP (I-III) 6. TMT 7. DST 8. DSST 9. VFT 	Cardiac surgery	Positive criteria for POCD is \geq tests from different areas.	POCD is reported to be 52% in control group and 46% in the study group.
Lewis M. S. <i>et al.</i> ; 2006 [14] (randomized, prospective)	204 patients	<ol style="list-style-type: none"> 1. Controlled Oral Word Association Task 2. DSST 3. GP Dominant Hand Condition 4. GP Non Dominant Hand 	By-pass surgery	1 DS in at least 2 tests	POCD varies between 13.3 and 49.4% POCD varies between 3.1 and 41.1% in the control group

		<p>Condition</p> <p>5. TMT A and B</p> <p>6. Consortium to Establish A Registry for Alzheimer's Disease</p> <p>7. Word Learning Task</p>			
Hansen M. V. <i>et al</i> ; 2012 [15] (prospective, multicentric)	976 patients enrolled, 271 included in the final study	<p>1. VVL</p> <p>2. Concept Shifting Task</p> <p>3. STROOP</p> <p>4. Letter Digit Coding</p>	Non-cardiac surgery	Mixed Z score >1.96 Individual Z score >1.96 in at least 2 tests	POCD was found in 93 patients out of 271 (34%)
Evered L. <i>et al</i> ; 2011 [16] (prospective)	644 patients + 34 patients in the control group	<p>1. Auditory Verbal Learning Test</p> <p>2. DSST</p> <p>3. TMT A and B</p> <p>4. Controlled Oral Word Association Test</p> <p>5. Consortium</p>	<p>1. Coronarography</p> <p>2. Hip arthroplasty</p> <p>3. Aorto-coronarian by-pass</p>	Reliable change index (RCI) < 1.96 Mixed Z score < 1.96 in at least 2 tests	POCD at day 7 in 17% from hip arthroplasty group, 43% in the by-pass group. At 3 months, POCD was found in 17% in both groups without

		<p>m to Establish a Registry for Alzheimer's Disease</p> <p>6. Verbal fluency – animals</p> <p>7. GP Dominant</p> <p>8. GP non dominant hand</p>			<p>statistical significant differences.</p>
<p>Ancelin M. L. <i>et al.</i>; 2010 [17] (prospective study)</p>	<p>270 patients + 320 patients from the control group</p>	<p>1. ECO</p> <p>2. DECO</p>	<p>Orthopedic surgery</p>	<p>POCD was defined as at least 1 point decrease from the baseline</p>	<p>POCD was defined as different cognitive models: Reaction time OR=1.74, p=0.01 Modeling time OR 3.6, p=0.0001 Geometric association OR=1.9, p=0.03 at postoperative day 8 POCD at 4 months distance OR=2.56,</p>

					<p>p<0.001</p> <p>POCD at 13 months</p> <p>OR=2.68,</p> <p>p<0.001</p> <p>Visual memory at 13 months</p> <p>OR=1.90,</p> <p>p=0.004</p>
<p>Hocker J. <i>et al.</i>; 2009 [18] (pilot study, randomized, double-blind)</p>	<p>101 patients</p>	<ol style="list-style-type: none"> 1. RAVLT 1-3 2. RAVLT LT 3. STROOP N1 4. STROOP N2 5. DST 6. DSST 7. PBT dominant 8. PBT non dominant 9. VFT semantic 10. VFT phonetic 	<p>Abdominal and urological surgery</p>	<p>POCD defined as 1 SD in at least 2 tests</p>	<p>POCD was found in 44% in xenon group vs. 50% in the Propofol group at postoperative day 1.</p> <p>POCD was found in 12% in xenon groups vs. 18% in the Propofol group at postoperative day 6.</p> <p>POCD was found in 6% in xenon group and 12% in Propofol group at postoperative day 30.</p>

<p>Ying-Hua Liu <i>et al.</i>; 2009 [19], (prospective cohort study)</p>	<p>227 patients</p>	<ol style="list-style-type: none"> 1. Mental control 2. Visual retention 3. Paired associate verbal learning 4. DST 5. DSST 6. TMT 7. GP dominant 8. GP non dominant hand 	<p>Aorto-coronarian by-pass with or without extra corporeal circulation (ECC)</p>	<p>Individual Z score > 1.96 Mixed Z score >1.96</p>	<p>POCD appreciated in 52% in the group with ECC vs. 47% in the group without ECC at 1 week distance after the surgery. POCD was found in 6.4% in the group with ECC and in 13.1% in the group without ECC at 3 months distance after the surgery.</p>
<p>Jensen B. O. <i>et al.</i>, 2008 [20] (randomized study)</p>	<p>120 patients</p>	<ol style="list-style-type: none"> 1. MMSE 2. VVL 3. Concept shifting test 4. STROOP 5. Letter-digit coding 	<p>Aorto-coronarian by-pass with or without extracorporeal circulation (ECC)</p>	<p>POCD appreciated as differences in at least 2 tests</p>	<p>POCD was 19% in the group without ECC and 9% in the ECC group. POCD defined as 20% decline in the cognitive score was found in 13% in the group without</p>

					<p>ECC and 12% in the ECC group.</p> <p>According to the Z score, POCD was found in 30% in the group without ECC and 28% in the ECC group.</p> <p>POCD at 3 and 12 months distance had no significant differences.</p>
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Note: *MMSE -Mini-Mental State Examination, TMT-Korean Trail-Making Test (or Trail-Making Test), GP-Grooved Pegboard, RAVLT rey's auditorial verbal learning test, RAVLT LT-rey's auditorial verbal learning, test long-term memory, GP (or PBT)- Grooved pegboard test performed (preferred hand, not dominant), STROOP- Stroop color word interference test, DST- Digit Span test, DSST-digit symbol substitution test, VFT-verbal fluency test, VVL-Visual Verbal Learning Test, ECO = Examen Cognitif par Ordinateur (evaluated on a computer), DECO - Détérioration Cognitive Observée*

Discussion

We identified 10 articles that fulfilled the criteria of the proposed aim. A large variety of diagnostic tools has been found that included 24 tests, with a mixture of them in 10 publications. The most common test used for POCD diagnosis was

Grooved pegboard test, which reflects visual and motor orientation areas [12, 13, 14, 16, 18, 19]. Evaluation of cognitive areas in publications is very variable, most of the authors used different questionnaires, but nevertheless not all of them cover all cognitive areas. Probably it is impossible to cover all cognitive areas without exhausting the patient, due to the fact that testing requires quite an amount of time.

Most of the studies were made on patients from cardiac surgery [13, 14, 16, 19, 20]. Cardiac surgery is very specific, patients being exposed to a higher risk of embolization or cerebral micro-embolization with thrombi formed due to extracorporeal circulation. Thus, patients have a higher risk for POCD. Other surgical fields, such as: abdominal and urological surgery [18], orthopedic surgery [11, 16, 17] and invasive procedures [17] are less studied. The small number of studies regarding POCD in other fields other than cardiac surgery suggests that extensive studies are required.

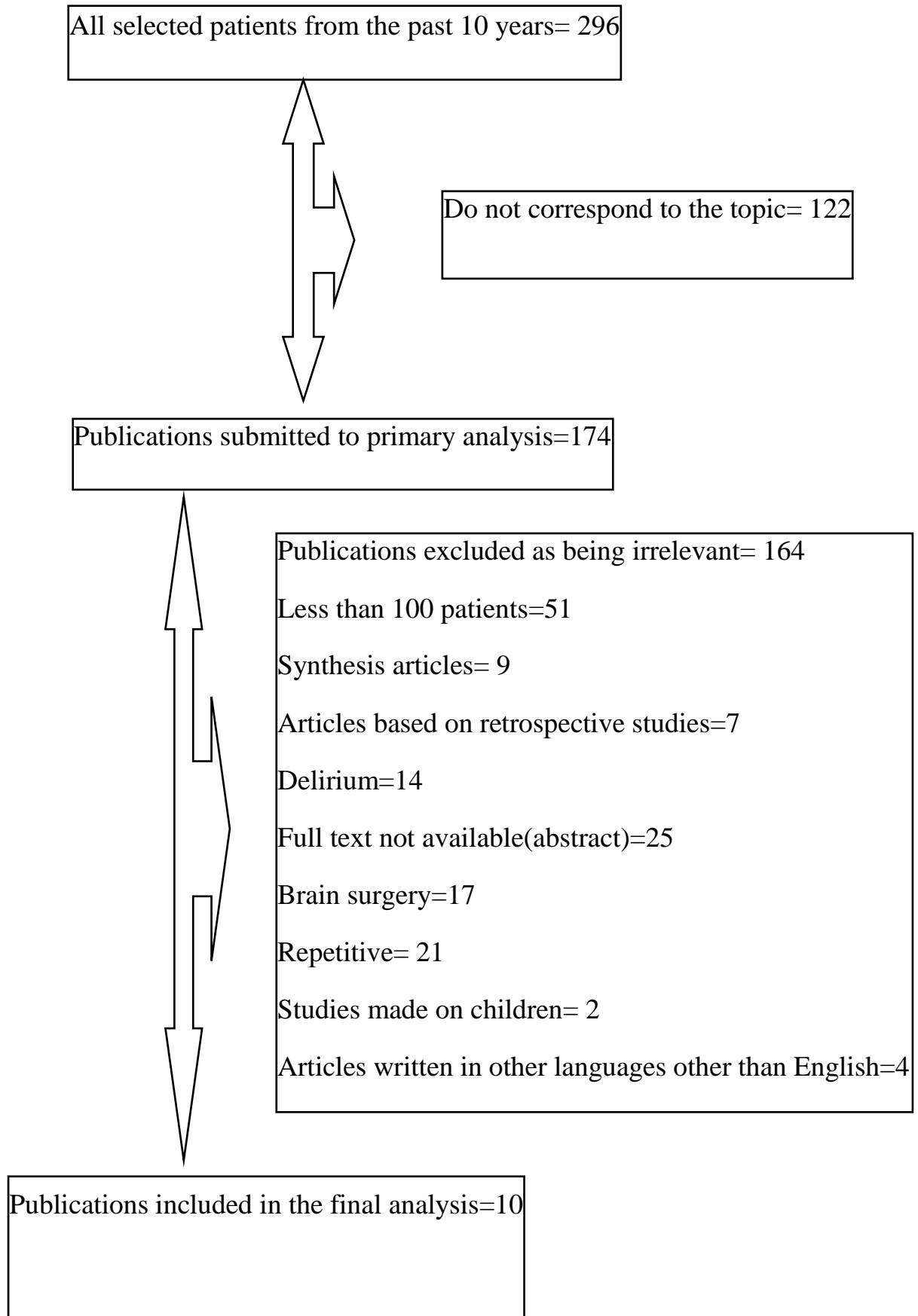
A series of articles were excluded from the final analysis due to a small number of enrolled patients. Probably these studies need to be made using a statistically relevant number of patients.

POCD varied between 3.1% and 52%. The reason of this large range of POCD's incidence relies in age differences of patients, type and duration of surgery, definition criteria of POCD (1, 2 or 3 questionnaires), way of interpretation of the results (standard deviation 1, 1.5, 2, Z score, RCI).

Conflict of interests

Nothing to declare

Fig. 1. Flow chart of publication selection.



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РЕЗЮМЕ

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ДІАГНОСТИЧНІ КРИТЕРІЇ ПІСЛЯОПЕРАЦІЙНОЇ КОГНІТИВНОЇ ДИСФУНКЦІЇ: ОГЛЯД ЛІТЕРАТУРИ

Вступ. Післяопераційна когнітивна дисфункція (РОСД) характеризується погіршенням когнітивних функцій (навчання, пам'яті, концентрації на об'єкті), які з'являються після анестезії та хірургічних втручань, Moller J. et al, 1998. [1]. Вперше, РОСД була описана у літніх людей в 1955 році Bedford P [2]. Особливість когнітивної системи полягає в її складності, яка вимагає безліч опитувальників для постановки діагнозу РОСД. До теперішнього часу, ідеальний тест або уніфікована методика використання опитувальників ще не створені. Таким чином, пропоновані опитувальники необхідно стандартизувати і оцінити їх валідність щодо РОСД з подальшим доказом їх ефективності та застосовності.

Матеріали і методи. Відповідні статті були знайдені в PubMed з використанням наступних ключових слів: післяопераційна когнітивна дисфункція, діагностичні критерії та оцінка. Для аналізу були представлені статті за останні 15 років.

Результати. Було знайдено 296 статей, які відповідали критерію включення, з них 10 статей стали предметом остаточного аналізу. В опублікованих статтях було знайдено 24 опитувальника по оцінці РОСД. Таким чином, в 6 дослідженнях [12, 13, 14, 16, 18, 19, 20] використовувалися Mini-Mental State Examination, Grooved pegboard test (preferred hand) і Grooved pegboard test (non dominant). У 5 дослідженнях [11, 13, 14, 15, 16, 18, 19, 20] були застосовані два опитувальники (STROOP - Stroop colour word difference test і DSST-digit symbol substitution test). Опитувальник TNM використовувався в 4 дослідженнях [12, 13, 14, 19]. The Visual Verbal Learning test, concept shifting test, letter digit coding, Digit Span Test були виявлені в трьох статтях [11, 13, 15,

18, 19, 20]. У двох дослідженнях представлені наступні опитувальні листи: Rey's auditorial verbal learning test (RAVLT), Rey's auditorial verbal learning test long-term memory (RAVLT-LT), verbal fluency test (VFT), visual verbal learning test (VVL), controlled oral word association test, consortium to establish a registry for Alzheimer's [13, 14, 16, 18]. В одному з досліджень було використано вісім опитувальників: Word Learning Task, Auditory Verbal Learning Test Digit, Disease verbal fluency-animals, Examen Cognitif par Ordinateur (ECO), Deterioration Cognitive Observee (DECO), Mental Control, Visual retention, Paired-Associate verbal learning [14, 16, 17, 19]. Згідно з думкою різних авторів, частота РОСД коливається від 3,1% до 52%.

Висновки. Велике розмаїття опитувальників, які використовуються для оцінки РОСД, призводить до двозначності в його діагностиці.

Ключові слова: дисфункція, когнітивні, післяопераційні.

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ДИАГНОСТИЧЕСКИЕ КРИТЕРИИ ПОСЛЕОПЕРАЦИОННОЙ КОГНИТИВНОЙ ДИСФУНКЦИИ: ОБЗОР ЛИТЕРАТУРЫ

Введение. Послеоперационная когнитивная дисфункция (РОСД) характеризуется ухудшением когнитивных функций (обучения, памяти, концентрации на объекте), которые появляются после анестезии и хирургических вмешательств, Moller J. et al, 1998 [1]. Впервые, РОСД была описана у пожилых людей в 1955 году Bedford P [2]. Особенностью когнитивной системы заключается в её сложности, которая требует множества опросников для постановки диагноза РОСД. До настоящего времени, идеальный тест или унифицированная методика использования опросников еще не созданы. Таким образом, предлагаемые опросники необходимо стандартизировать и оценить их валидность в отношении РОСД с дальнейшим доказательством их эффективности и применимости.

Материалы и методы. Соответствующие статьи были найдены в PubMed с использованием следующих ключевых слов: послеоперационная когнитивная дисфункция, диагностические критерии и оценка. Для анализа были представлены статьи за последние 15 лет.

Результаты. Было найдено 296 статей, которые соответствовали критерия включения, из них 10 статей стали предметом окончательного анализа. В опубликованных статьях было найдено 24 опросника по оценке ПОСД. Таким образом, в 6 исследованиях [12, 13, 14, 16, 18, 19, 20] использовались Mini-Mental State Examination, Grooved pegboard test (preferred hand) и Grooved pegboard test (non dominant). В 5 исследованиях [11, 13, 14, 15, 16, 18, 19, 20] были применены два вопросника (STROOP – Stroop colour word difference test и DSST-digit symbol substitution test). Опросник TNM использовался в 4 исследованиях [12, 13, 14, 19]. The Visual Verbal Learning test, concept shifting test, letter digit coding, Digit Span Test были обнаружены в трех статьях [11, 13, 15, 18, 19, 20]. В двух исследованиях представлены следующие опросные листы: Rey's auditorial verbal learning test (RAVLT), Rey's auditorial verbal learning test long-term memory (RAVLT-LT), verbal fluency test (VFT), visual verbal learning test (VVL), controlled oral word association test, consortium to establish a registry for Alzheimer's [13, 14, 16, 18]. В одном из исследований было использовано восемь опросников: Word Learning Task, Auditory Verbal Learning Test Digit, Disease verbal fluency-animals, Examen Cognitif par Ordinateur (ECO), Deterioration Cognitive Observee (DECO), Mental Control, Visual retention, Paired-Associate verbal learning [14, 16, 17, 19]. Согласно мнению различных авторов, частота ПОСД колеблется от 3,1% до 52%.

Выводы. Большое разнообразие опросников, используемых для оценки ПОСД, приводит к двусмысленности в его диагностике.

Ключевые слова: дисфункция, когнитивные, послеоперационные.

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DIAGNOSTIC CRITERIA FOR POST-OPERATIVE COGNITIVE DYSFUNCTION: LITERATURE REVIEW

Introduction. Postoperative cognitive dysfunction (POCD) is characterized by deterioration of cognitive performances (learning, memory, focusing) that appears after anesthesia and surgery, Moller J. *et al*, 1998 [1]. For the first time, POCD was described in elderly persons in 1955 by Bedford P [2]. The peculiarity of the cognitive system is its complexity that requires a large variety of questionnaires in order to assess POCD. An ideal test or a unification of questionnaires has not been made yet. Thus, the proposed questionnaires need to be standardized and validated for POCD assessment with further proof of its utility and applicability.

Material and methods. Relevant articles have been searched in PubMed using the following key words: postoperative cognitive dysfunction, diagnostic criteria, assessment and evaluation. Articles from the last 15 years have been submitted for analysis.

Results. A number of 296 of articles have been identified, according to inclusion criteria, out of them, 10 articles were subject of final analysis. In the published articles, 24 questionnaires regarding POCD assessment were found. Thereby, Mini-Mental State Examination, Grooved pegboard test (preferred hand) and Grooved pegboard test (non dominant) were used in 6 studies [12, 13, 14, 16, 18, 19, 20]. Two questionnaires (STROOP – Stroop colour word difference test and DSST-digit symbol substitution test) were applied in 5 studies [11, 13, 14, 15, 16, 18, 19, 20]. The TNM questionnaire was used in 4 researches [12, 13, 14, 19]. The Visual Verbal Learning test, concept shifting test, letter digit coding, Digit Span Test were all identified in 3 articles [11, 13, 15, 18, 19, 20]. Two researches contain the following questionnaires: Rey's auditorial verbal learning test (RAVLT), Rey's auditorial verbal learning test long-term memory (RAVLT-LT), verbal fluency test (VFT), visual verbal learning test (VVL), controlled oral word association test, consortium to establish a registry for Alzheimer's [13, 14, 16, 18]. Eight questionnaires were used by a single research: Word Learning Task, Auditory Verbal Learning Test Digit, Disease verbal fluency-animals, Examen Cognitif par Ordinateur (ECO),

Deterioration Cognitive Observee (DECO), Mental Control, Visual retention, Paired-Associate verbal learning [14, 16, 17, 19]. According to different authors, POCD varies between 3.1% and 52%.

Conclusions. A big variety of questionnaires used in POCD appreciation leads to ambiguity in its diagnosis.

Key words: dysfunction, cognitive, postoperative.

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