Identification of Risk Factors for Delirium, Cognitive Decline, And Dementia After Cardiac Surgery (FINDERI - Find Delirium Risk Factors): A Study Protocol of A Prospective Monocentric Observational Pilot Trial

Monika Sadlonova (✉ monika.sadlonova@med.uni-goettingen.de)

University Medical Center Göttingen: Universitätsmedizin Göttingen <https://orcid.org/0000-0003-3629-252X>

Jonathan Vogelgsang

McLean Hospital

Claudia Lange

University Medical Center Göttingen: Universitätsmedizin Göttingen

Irina Günther

University Medical Center Göttingen: Universitätsmedizin Göttingen

Adriana Wiesent

University Medical Center Göttingen: Universitätsmedizin Göttingen

Charlotte Eberhard

University Medical Center Göttingen: Universitätsmedizin Göttingen

Julia Ehrentraut

University Medical Center Göttingen: Universitätsmedizin Göttingen

Mareike Kirsch

University Medical Center Göttingen: Universitätsmedizin Göttingen

Niels Hansen

University Medical Center Göttingen: Universitätsmedizin Göttingen

Hermann Esselmann

University Medical Center Göttingen: Universitätsmedizin Göttingen

Charles Timäus

University Medical Center Göttingen: Universitätsmedizin Göttingen

Thomas Asendorf

University Medical Center Göttingen: Universitätsmedizin Göttingen

Benedict Breitling

University Medical Center Göttingen: Universitätsmedizin Göttingen

Mohammed Chebbok

University Medical Center Göttingen: Universitätsmedizin Göttingen

Ingo Kutschka

University Medical Center Göttingen: Universitätsmedizin Göttingen

Jens Wiltfang

University Medical Center Göttingen: Universitätsmedizin Göttingen

Hassina Baraki

University Medical Center Göttingen: Universitätsmedizin Göttingen

Christine A.F. von Arnim

University Medical Center Göttingen: Universitätsmedizin Göttingen

Study Protocol

Keywords: delirium, cognitive decline, dementia, delirium screening, cardiac surgery, biomarkers

Posted Date: September 8th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-812268/v1>

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

[Read Full License](#)

Abstract

BACKGROUND: Postoperative delirium is a common complication of cardiac surgery associated with higher morbidity, longer hospital stay, risk of cognitive decline, dementia, and mortality. Geriatric patients, patients undergoing cardiac surgery, and intensive care patients are at a high risk of developing a postoperative delirium. A gold standard assessment or biomarkers to predict risk factors for delirium, cognitive decline, and dementia in patients undergoing cardiac surgery are not yet available.

METHODS: The FINDERI trial (FINd DELirium RIsk factors) is a prospective, single-center, observational pilot study. In total, 500 patients aged ≥ 50 years undergoing cardiac surgery at the Department of Cardiovascular and Thoracic Surgery of the University of Göttingen Medical Center will be recruited. Our primary aims are to validate a delirium screening questionnaire and to identify specific preoperative risk factors and perioperative exposition factors for postoperative delirium, cognitive decline, and accelerated dementia after cardiac surgery. Our secondary aim is to identify blood-based biomarkers that predict the incidence of postoperative delirium, cognitive decline, or dementia in the context of cardiac surgery.

CONCLUSION: This prospective, observational pilot trial might help to identify pre- and perioperative risk factors and biomarkers for postoperative delirium, cognitive decline, and dementia. The predictive value of a delirium screening questionnaire in cardiac surgery might also be revealed.

TRIAL REGISTRATION: Ethics approval for this study was obtained from the IRB of the University of Göttingen Medical Center. The investigators registered this study in German Clinical Trials Register (DRKS) (DRKS00025095) on April, 19th 2021 https://www.drks.de/drks_web/navigate.do?navigationId=trial.HTML&TRIAL_ID=DRKS00025095.

Background

Postoperative delirium (POD) is a common complication of cardiac surgery associated with poorer outcomes [1, 2]. Several studies have already shown that geriatric patients, patients undergoing cardiac surgery, and intensive care patients are at a high risk of developing POD [3–9]. Recent data suggests an age-dependent incidence of post-cardiac surgery delirium: 21.4% of patients aged ≥ 65 suffered from POD, and POD was observed in 33.5% of patients aged > 80 [1]. The severity of a medical disability, as indicated by the medical treatment setting, affects the risk of delirium: for intensive care units (ICU, 83.3%, odds ratio [OR] 12.34), and intermediate care units (IMC, 39.8%, OR 1.42) [10]. In that study, patients with delirium were hospitalized twice as long (14.3 vs. 7.7 days), were more likely to have pre-existing dementia, and were more likely to die in hospital [10]. A meta-analysis including almost 2,939 patients showed that delirium is associated with an increased risk of death after an average follow-up of 22.7 months (HR 1.95, 95% CI 1.51–2.52), and an increased risk of institutionalization (OR 2.41, 95% CI 1.77–3.29) [11]. In several studies, delirium was associated with an increased risk of postoperative cognitive dysfunction and dementia [10–12]. For example, a recent study showed an association between delirium

severity and subsequent 3-year cognitive impairment [13]. In patients who experienced the most severe delirium, the rate of cognitive decline nearly tripled [13].

It has recently been shown that surgery, in particular cardiac surgery, is associated with increased markers for neuronal damage and neurodegeneration, such as total-Tau and neurofilament light chain (NFL) [14–17]. In fact, these effects, including hypoxemia and disruption of the blood-brain barrier, seem to be caused by the entire procedure and not solely by inhalational anesthesia, as discussed earlier [18]. It is likely that patients with an underlying neurodegenerative disorder, although still clinically inapparent, might experience a significant “second hit” that accelerates the neurodegenerative processes causing cognitive decline after these interventions. This hypothesis is supported by pre-surgery cerebrospinal fluid (CSF) measurements of Amyloid- β_{42} ($A\beta_{42}$), a key biomarker for Alzheimer’s disease (AD) [19]. Furthermore, Evered et al. report decreased CSF $A\beta_{42}$ levels in patients suffering from cognitive decline after general surgery [19].

Most studies of biomarkers in delirium are related to an inflammatory response. The interaction between systemic and brain inflammation is discussed and the association of inflammatory biomarkers like C-reactive protein (CRP) and delirium has been shown in critically ill patients, but also other etiologies [20]. Recently published studies showed that a significant increase in the inflammatory markers CC-chemokine ligand 2 (CCL2) [21], interleukin-6 (IL-6) [22], fibroblast growth factor (FGF) 21 and 23 [23] is associated with POD following cardiac surgery. The association between the neuroinflammatory marker, glial fibrillary acidic protein (GFAP) plasma levels, and POD has been analyzed in several studies [24]. GFAP plasma levels are known to be elevated in cases with astroglial damage [25], and neurodegenerative processes such as AD [26–30]. Therefore, GFAP might exhibit a link between inflammation and neurodegeneration.

The ability to identify patients at risk prior to surgery is essential for delirium prevention and advanced care planning [31]. In previous research, preoperative and pre-existing risk factors of delirium in patients undergoing cardiac surgery, as well as perioperative and intraoperative risk factors of delirium, were analyzed. For example, a study analyzing 1,206 patients undergoing open-heart surgery identified higher age and longer aortic cross-clamp time as important risk factors for POD [32]. Furthermore, a retrospective analysis of 1,797 patients identified eight independent factors for the development of post-cardiac surgery delirium: age, low ejection fraction, diabetes, extracardiac arteriopathy, postoperative atrial fibrillation, pneumonia, elevated creatinine, and prolonged hospitalization stay. Additionally, these independent factors are all markers for pre-interventional frailty [1]. However, these studies did not distinguish between pre-existing risk factors that can identify patients with high risk for delirium and peri- and intraoperative factors that can have the potential for modified operative approaches. From a clinical point of view, this is an important distinction.

While there are well-established predictors for delirium incidence, a standardized screening assessment for the risk of POD is not available [33–35]. Lindroth et al. [31] examined numerous assessments for delirium prediction. Overall, a measure of executive function, Trail Making Test B (TMTB), and risk score

of the American College of Surgeons (ACS), National Surgical Quality Improvement Program (NSQIP) for serious complications predicted POD severity using advanced modeling techniques [31]. However, further research is needed to establish a reliable and time-efficient screening instrument for delirium into the preoperative daily routine of cardiac surgery.

The main aims of this study are: a) to validate a delirium screening questionnaire, b) to identify specific preoperative risk factors and perioperative exposure factors for POD, cognitive decline, and accelerated dementia after cardiac surgery, c) to identify blood-based biomarkers that predict the incidence of POD, cognitive decline or dementia in the context of cardiac surgery.

Methods

Study design

FINDERI is a prospective, single-center, observational pilot trial. The primary hypothesis is to validate a delirium screening questionnaire for POD. The primary hypothesis is to validate a delirium screening questionnaire for POD. Secondary, the study aims to identify specific pre- and perioperative risk factors and biomarkers for POD and cognitive decline in patients undergoing cardiac surgery, and to investigate if cardiac surgery accelerates a cognitive decline in the presence of A β pathology. Ethical approval for the study was obtained from the IRB of the University of Göttingen Medical Center (#20/11/20). The investigators registered this study in German Clinical Trials Register (DRKS) (DRKS00025095) on April, 19th 2021

Study setting and participants

In total, 500 patients aged over 50 years old undergoing cardiac surgery will be recruited at the Department of Cardiovascular and Thoracic Surgery of the University Medical Center Göttingen, Germany. Inclusion and exclusion criteria are summarized in Table 1. Potentially eligible participants are identified by preoperative schedules. Informed consent will be collected after provided detailed study information and prior to baseline assessment and biomarker sampling. Initially, the preoperative screening will be provided via medical history, screening questionnaire, and laboratory measurement for identification of risk factors for delirium, cognitive decline, and dementia (t0). Furthermore, delirium screening will be assessed over the first five postoperative days (t1) and biomarkers will be measured on the 7th postoperative day (t2) to address the impact on neurodegenerative and neuroinflammatory markers after cardiac surgery. We will provide a follow-up visit of patients with a verified diagnosis of POD 3 to 5 months after cardiac surgery (t3), follow-up of all patients on phone 12 months after surgery (t4), and follow-up of patients with a verified diagnosis of POD 18 months after surgery (t5) (Fig. 1, Table 2).

Preoperative screening (t0)

Upon admission, a preoperative delirium screening is carried out using a questionnaire (**Supplement 1**) developed in the context of the multicenter cluster-randomized PAWEL study[36] on the reduction of delirium risk and postoperative cognitive dysfunction after elective procedures in older adults. The preoperative screening questionnaire includes the following assessment: A) Geriatric check (mobility, statutory level of independency, cognition, psychological symptoms, and previous hospital stay); B) Short 6-item cognitive screening; C) General information including results from A) and B) as well as age > 80, laboratory measurement such as increased creatine, CRP, hemoglobin, decreased protein, American Society of Anesthesiologists (ASA) score ≥ 3 [37]. The patient's current medications are also noted; however, particular attention is paid to the number of medications and medications with a deliriogenic risk. Furthermore, pre-surgical diagnosis of depression, stroke, dementia, and previous hospital stays within the last year will be assessed. In addition, it is checked whether a care level exists and whether the patient is a nursing home resident. The patient is asked about previous delirium and a recent increase in number of falls. Another component of the survey is the self-reported subjective memory impairment (SMI), alcohol use, and smoking status. Finally, the patient's handgrip strength will be measured by Jamar® Hydraulic Hand Dynamometer.

Furthermore, the following variables will be evaluated by trained assessors for baseline assessments (**Supplement 2**). Basic sociodemographic information will be collected, including marital status, number of children, immigrant background, educational level, occupation, living arrangement, and care level. Moreover, an examination of previous cardiac and noncardiac comorbidities will be provided. Frailty will be assessed using the 7-point Clinical Frailty Scale of the Canadian Study of Health and Aging (CSHA Frailty Scale, 1-very fit up to 7-severely frail) [38]. In addition, the outcome-oriented nursing assessment instrument AcuteCare 1.1 (ePA-AC) [39], whereby the software generates a delirium risk score and a self-care score, will be assessed from the MEONA software. Factors biasing the adequate elicitation of the ePA-AC (**Supplement 3**), such as the understaffing of nurses, will be documented.

The pre-surgical cognitive status will be measured using neuropsychological screening, including Montreal Cognitive Assessment (MoCA), Trail Making Test A, and Trail Making Test B (TMTA, TMTB). MoCA is a 30-point brief cognitive screening with the following subscales: short-term memory recall task (5 points), visuospatial abilities (5 points), executive functions (4 points), attention, concentration, and working memory (5 points), language (5 points), orientation to time and place (6 points). The MoCA has high sensitivity (0.90) and specificity (0.87) to detect patients with mild cognitive impairment [40]. TMT is a widely used neuropsychological instrument to assess the speed of cognitive processing, visuomotor tracking, divided attention, and cognitive flexibility [34, 41–43]. The test consists of two parts (A and B). In part A, patients are instructed to draw lines connecting consecutively numbered circles from 1 to 25 in ascending order. In part B, the circles include both numbers (1–13) and letters (A-L), and the patients draw lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters. Total time will be recorded in seconds. In elderly volunteers, part B had a specificity of 0.89, and sensitivity of 0.63 for cognitive dysfunction, and 0.72 for dementia [34, 41–43].

Finally, blood samples will be measured before the surgery to address the hypotheses and predictive values of serum biomarkers for delirium, cognitive decline, and early-onset dementia. This examination section will take approximately 60 minutes.

Delirium screening (t1) and postoperative laboratory measurements (t2)

All study patients will be assessed twice a day using the Confusion Assessment Method (CAM) on the intensive care unit (CAM-ICU) or I-CAM on the intermediate care unit. CAM is a four features diagnostic algorithm for delirium screening at the bedside with a rating of acute onset or symptom fluctuation, inattention, disorganized thinking, and altered level of consciousness. I-CAM has a high sensitivity of 0.77 in a cohort of geriatric patients with a high prevalence of dementia and a specificity of 0.96-1.00 with inter-rater reliability of Cohen's kappa 0.95. CAM-ICU is an adaptation of I-CAM for critically ill patients on or off the ventilator. The first step in assessing delirium in ICU is the Richmond Agitation-Sedation Scale (RASS), followed by the four features of the I-CAM with an extra assessment of pictures in feature 2 if patients are not able to complete letters. CAM-ICU shows a high sensitivity of 0.95-1.00 and specificity of 0.89–0.93 with inter-rater reliability of Crohn's kappa from 0.88 to 1.0 [44–47]. Since POD symptoms often occur at night, chart reviews[48] (**Supplement 4**) will be assessed for the first five postoperative days. This section of the investigation will take approximately 10–15 minutes per survey. Blood will be sampled again on the 7th postoperative day (t2). Finally, a surgery protocol using the data from cardiac surgery and anesthesiology will be collected using the following data: type of cardiac surgery, time of surgery (cut-to-suture-time), aortic cross-clamp time, intraoperative complications, and use/time of the heart-lung machine.

Neurocognitive assessments (t3)

Patients suffering from POD within 5 postoperative days will be asked to continue the study for additional follow-up visits (3 to 5 months after cardiac surgery) for in-depth memory assessments (t3). They will undergo a standardized neuropsychological investigation. Neuropsychological assessments are performed to evaluate the patients' neurocognitive stage to define different stages of cognitive decline, namely mild cognitive impairment or dementia. A diagnosis of dementia (DSM-5: major neurocognitive disorder) or mild cognitive impairment (DSM-5: mild neurocognitive disorder) is made according to the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [49]. A neuropsychological battery will be applied to determine cognitive impairment or early dementia (Table 3): MoCA, Subtests of the Wechsler Adult Intelligence Scale IV (WAIS-IV: Block Design, Digit Span forward and backward, Coding), subtests of the Wechsler Memory Scale IV (WMS-IV: Logical Memory I and II, Visual Reproduction I and II), the Rey-Osterrieth Complex Figure Test (RCFT), the CERAD (Consortium to Establish a Registry for Alzheimer's Disease)-Plus test battery (including Trail Making Test A and B and

letter fluency), clock drawing test and a test of ideomotor apraxia (imitation of finger gestures) by Goldenberg. The estimated time for full neuropsychological testing will be approximately 75 minutes.

Test results will be discussed with a physician at the memory clinic at the Department of Psychiatry and Psychotherapy of the University of Göttingen Medical Centre. If indicated, additional diagnostic procedures will be offered to determine a clinical diagnosis. Neuropsychiatric symptoms will be measured using established and standardized questionnaires and external rating scales, depending on the clinical presentation. The following instruments (Table 4) can be used: Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS), REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ), Neuropsychiatric Inventory (NPI), and Scale for the Assessment of Positive Symptoms (SAPS). In addition, another blood sample is taken.

Follow up (T4 after 12 months and T5 after 18 months)

One year after the cardiac surgery, all patients (with and without delirium after cardiac surgery) will be contacted via phone to evaluate any new onset of neurological disorders, deterioration of cognitive decline using MoCA or physical autonomy, and current medications. Furthermore, previous COVID-19 infection and vaccination status will be assessed. The telephone interview will take approximately 30 minutes.

After 18 months, another standard neuropsychological examination will be provided in hospital for patients with a verified diagnosis of POD after cardiac surgery. This visit is comparable with the t3 visit, including standard neuropsychological battery for assessment of cognitive impairment or early dementia (Table 3), and neuropsychiatric symptoms questionnaire depending on the clinical presentation (Table 4).

Blood sampling and biomarker measurements

Blood sampling and biomarker analysis are some of the main goals and hypotheses of this study. Up to 50 ml of blood per study visit (t0, t2, t3, t5) will be sampled. Blood collection (serum, plasma, RNA out of PAXgene tubes), processing, and storage will be performed according to local established SOPs. Serum and plasma will be briefly kept at 4°C until processing. Serum will be stored for 45 minutes for coagulation. Serum and EDTA-plasma will be centrifugated for 10 minutes at 2,000 x g and stored as 500µl aliquots at -80°C. The cellular pellet from the EDTA-tube will be reconstituted in PBS and stored at -80°C for DNA extraction. PAXgene tube will be stored for 120 minutes at room temperature, followed by 24 hours at -20°C and long-term storage at -80°C until use. The investigation is initially designed as a prospective single sample survey and longitudinal data collection. With the help of various protein-analytical or other measurement methods, new biomarkers for POD, cognitive decline, and dementia will be identified and validated. In addition to proteomic or metabolomic markers, genomic and epigenetic markers, such as the ApoE genotype, will be examined. The test persons are therefore explicitly advised that a genetic examination of the donated material may be carried out. To protect the participants, no

feedback is given about individually achieved markers, in particular predictive markers. To test our hypothesis that pre-surgical Alzheimer's pathology is a risk factor to develop POD followed by cognitive decline, we will measure plasma A β using our recently developed two-step immunoassay [65, 66], p-tau181 [67, 68], NfL [69, 70], and GFAP[26] using SIMOA technology [71, 72]. Samples will be handled according to our recently published SOP suggestions to minimize pre-analytical effects on plasma A β [73]. As POD and cognitive decline are often considered to be associated with a concomitant increase in inflammatory cytokines, we want to identify markers that correlate with delirium and neurodegenerative markers. Therefore, we will also analyze a cytokine panel, including IL-1ra-, IL-6, IL-8, IL-10, and tumor necrosis factor (TNF) alpha [23, 74–76]. Furthermore, to overall understand the impact of specific cardiovascular alteration and to test the hypothesis that changes in cardiovascular markers are associated with delirium, we analyze the cardiovascular marker growth differentiation factor 15 (GDF-15) [77].

Study sample

In order to plan a subsequent confirmatory study, it is necessary to estimate the necessary parameters with sufficient accuracy. The sample size planning is based specifically on estimating the area under the curve (AUC) of the delirium short screening for the occurrence of delirium with a 95% confidence interval so that the 95% confidence interval has a width of approximately 0.05 points. It is assumed that the prevalence of POD is 50% and that there is a true AUC of 0.7. In 416 patients analyzed, the 95% confidence interval extends approximately 0.025 points from the estimate. In order to compensate for possible dropouts (assumed dropout rate approx. 20%), 500 patients are therefore recruited. The calculation was done in nQuery 8.

Statistical analysis

In order to determine the prognostic properties of constant endpoints and questionnaire scores to predict the development of POD, as well as postoperative cognitive decline, Alzheimer's dementia, and prognostic quality measures are calculated. Specifically, an ROC curve of the observations with the associated AUC with optimal cut-off point (simultaneous maximization of sensitivity and specificity, as well as according to Youden) will be performed. Furthermore, positive and negative predictive values for the optimal cut-off point and the observed incidence risk factors for the development of POD, cognitive decline, and Alzheimer's or Lewy body dementia will be investigated using logistic regression and effect sizes are reported as hazard ratios. As far as possible, all key figures are given with a 95% confidence interval. In addition to the univariate consideration of the individual parameters, a multivariate consideration of predictive factors is also planned. For this purpose, several machine learning methods (supervised learning) are trained on a training data set (70% of the data collected) and their accuracy is compared with a test data set (30% of the data collected). The division into test and training data sets is random.

Data management

All outcomes are entered into a Good Clinical Practice (GCP) compliant database (secuTrial®), configured for this trial. The configuration includes univariate checks for plausibility, such as range checks. Data are regularly reviewed for completeness by qualified personnel and locked after review. A blinded data review (without knowledge on the development of delirium) to assess data quality is performed prior to database lock. After database lock, the data set is archived for at least 10 years on a digital medium within the trial master file. An anonymized copy of the data set is provided alongside the publication to ensure the reproducibility of results. The investigators follow the Findability, Accessibility, Interoperability, and Reuse (FAIR) Guiding Principles for scientific data management and stewardship.

Discussion

Postoperative delirium is a common complication of cardiac surgery associated with prolonged hospitalization, a higher complication rate, increased risk of cognitive decline, dementia, and mortality [10–12]. Geriatric patients, patients after cardiac surgery, and intensive care patients are at a high risk of developing POD [3–7, 9]. Additionally, previous research shows an increase in neurodegenerative and neuroinflammatory markers after cardiac surgery [14, 16]. The ability to identify moderate to high risk patients prior to surgery is essential for delirium prevention [31]. While there are well-established predictors for delirium incidence, an established standard assessment or measurement of a biomarker for risk of POD and its severity is not available [33, 35, 36]. Further research is needed to establish a reliable screening instrument and measurements of biomarkers for risk of POD, cognitive decline, or dementia in patients undergoing cardiac surgery.

FINDERI is a prospective, single-center, observational pilot study. In total, 500 patients aged over 50 undergoing cardiac surgery will be recruited at the Department of Cardiovascular and Thoracic Surgery of the University Medical Center Göttingen, Germany. The data collection for the patient extends over t0 at the time of admission (preoperative screening), over t1 on the 1st-5th postoperative days (delirium screening), t2 on the 7th postoperative day (laboratory measurements), as well as inpatient via t3 after 3 to 5 months, t4 after 12 months postoperatively and t5 after 18 months postoperatively.

The main aim of our study is a) to analyze the reliability, sensitivity, and specificity of a delirium screening questionnaire, b) to identify risk factors for postoperative delirium, cognitive decline, and accelerated dementia after cardiac surgery, c) to identify serum biomarkers that predict the incidence of postoperative delirium, cognitive decline or dementia.

An early identification of patients at a high risk for delirium and cognitive decline can potentially help to implement a specific non-pharmacological interventions for delirium prevention [34, 78]. Furthermore, by identifying expositional factors perioperative and surgical procedures can also be individually tailored.

Our FINDERI study design has several strengths such as the longitudinal design with one year follow up, highest standards for delirium detection using CAM, CAM-ICU, and chart review, or analyzing a broad and

representative population. However, this study has several limitations. We will focus our primary and secondary hypotheses on identifying pre- and perioperative delirium risk factors, and not on the impact of delirium on morbidity, mortality, and hospital utilization of patients undergoing cardiac surgery or its treatment. Second, we will enroll only patients with POD to neurocognitive screening 3–5 months after surgery. Our control group for assessing cognitive decline and dementia in all participants will be interviewed 12 months after their surgery by phone. Third, further research will be needed to replicate our findings in a larger multicenter, prospective, observational study.

Abbreviations

A β ₄₂: Amyloid- β ₄₂; ACS: American College of Surgeons; AD: Alzheimer's disease; ASA: American Society of Anesthesiologists; AUC: area under the curve; CAM: Confusion Assessment Method; CCL2: CC-chemokine ligand 2; CERAD: Consortium to Establish a Registry for Alzheimer's Disease; CRP: C-reactive protein; CSHA: Canadian Study of Health and Aging; CSF: cerebrospinal fluid; DRKS: German Clinical Trials Register; DSM-5: Diagnostic and Statistical Manual of Mental Disorders; ePA-AC: AcuteCare 1.1; FAIR: Findability, Accessibility, Interoperability, and Reuse; FGF: fibroblast growth factor; GCP: Good Clinical Practice; GFAP: glial fibrillary acidic protein; GDF: growth differentiation factor; ICU: intensive care unit; IL-6: interleukin-6; IMC: intermediate care unit; MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale; MoCA: Montreal Cognitive Assessment; NFL: neurofilament light; NPI: Neuropsychiatric Inventory; NSQIP: National Surgical Quality Improvement Program; OR: odd ratio; POD: Postoperative delirium; RASS: Richmond Agitation-Sedation Scale; RBDSQ: REM Sleep Behavior Disorder Screening Questionnaire; RCFT: Rey-Osterrieth Complex Figure Test; SAPS: Scale for the Assessment of Positive Symptoms; SMI: subjective memory impairment; TMTA: Trail Making Test A; TMTB: Trail Making Test B; TNF: tumor necrosis factor; WAIS: Subtests of the Wechsler Adult Intelligence Scale IV; WSM: Wechsler Memory Scale IV.

Declarations

Ethics approval and consents to participate

This study protocol, Version 2, was approved by the Ethics Committee of the University of Göttingen Medical Center on February 2, 2021 (#20/11/20). Patient recruitment only started after ethical approval has become available at the respective sites. Study staff explains study procedures to patients in detail, and gives patients enough time and opportunity to obtain answers to any open questions. Patients are informed that their participation is voluntary and that they may withdraw at any time without having to give reasons and without penalty or loss of benefits to which they are otherwise entitled. In addition, the patient receives a "patient consent form and patient information sheet", which contains all the important information about the study in writing. Written informed consent is obtained from each participant before any trial-related procedures are performed and patients receive a copy of the signed and dated written consent form.

Consent for publication

Not applicable.

Availability of data and materials

Research data will be stored and managed at the UMG. The anonymized original data set will be published in a certified data repository for future use after completion of the trial and acceptance of the primary results publication. The principal investigator will form a subgroup for approving requests from external researchers to access the data. The investigators follow the FAIR Principles for scientific data management and stewardship.

Competing interests

MS, IG, AW, CE, JE, JV, NH, HE report no competing interest. JW has served at scientific advisory boards for Abbot, Biogen, Boehringer-Ingelheim, Eli Lilly, F. Hoffmann-La Roche, Immungenetics, MSD SHARP & DOHME, has received honorarium for lectures sponsored by Eli Lilly, Pfizer, Janssen, MSD SHARP & DOHME, Amgen, Roche Pharma, Actelion Pharmaceuticals, Guangzhou Glorylen Medical Technology Co. (China), Beijing Yibai Science and Technology Ltd. CAFvA received honoraria from serving on the scientific advisory board of Biogen, Roche, and Dr. Willmar Schwabe GmbH &Co. KG and has received funding for travel and speaker honoraria from Biogen, Roche diagnostics AG and Dr. Willmar Schwabe GmbH &Co. KG and has received research support from Roche diagnostics AG.

Funding

Open access funding enabled and organized by the Open Access Publication Funds of the University of Göttingen. This trial is self-funded by the Department of Cardiovascular and Thoracic Surgery, the Department of Psychiatry and Psychotherapy, and the Department of Geriatrics of the University of Göttingen Medical Centre, Germany. MS receives funding for her research fellowship at Massachusetts General Hospital and Harvard Medical School, Boston, USA from the German Heart Foundation. JV received funding by the Eric Dorris Memorial Fund and the NIH P50. JW is supported by an Ilídio Pinho professorship, iBiMED (UIDB/04501/2020) at the University of Aveiro, Portugal.

Trial governance

FINDERI is coordinated at the University of Göttingen Medical Centre (UMG) and supported by the UMG clinical trial unit (RT), where the data are hosted and managed. It is governed by a trial steering committee, consisting of the coordinating investigator (MS), the investigator at the Department of Cardiovascular and Thoracic Surgery (HB), the investigator at the Division of Geriatrics (CvA), the investigator at the Department of Psychiatry and Psychotherapy (JW), and the biostatistician (TA).

Authors' contributions

MS, CAFvA, HB, JW, JV and CL have developed the overall study concept. MS and JV have drafted the text of the study protocol with support from CL, IG, JE, CE, AW, BB, TA, CAFvA. The draft manuscript was reviewed by all authors and discussed during telephone and videoconferences and comments from all authors were taken up and integrated. All authors have read and approved the final manuscript.

Acknowledgements

The authors wish to thank Anke Jahn-Brodmann for training and supervision according to measurement of biomarkers. The authors gratefully acknowledge the contributions of the patients, family members, nurses, physicians, staff members, and the FINDERI study group. We acknowledge support by the Open Access Publication Funds of the University of Göttingen.

References

1. Kotfis K, Szylińska A, Listewnik M, Strzelbicka M, Brykczyński M, Rotter I, et al. Early delirium after cardiac surgery: an analysis of incidence and risk factors in elderly (≥ 65 years) and very elderly (≥ 80 years) patients. *Clin Interv Aging*. 2018;13:1061–70. <https://doi.org/10.2147/CIA.S166909>.
2. Smulter N, Linge Hall HC, Gustafson Y, Olofsson B, Engström KG. Delirium after cardiac surgery: incidence and risk factors. *Interact Cardiovasc Thorac Surg*. 2013;17(5):790–6. <https://doi.org/10.1093/icvts/ivt323>.
3. Krewulak KD, Stelfox HT, Ely EW, Fiest KM. Risk factors and outcomes among delirium subtypes in adult ICUs: A systematic review. *J Crit Care*. 2020;56:257–64. <https://doi.org/10.1016/j.jcrc.2020.01.017>.
4. Inouye SK, Westendorp RGJ, Saczynski JS. Delirium in elderly people. *The Lancet*. 2014;383(9920):911–22. [https://doi.org/10.1016/S0140-6736\(13\)60688-1](https://doi.org/10.1016/S0140-6736(13)60688-1).
5. Zhang W, Wu W, Gu J, Sun Y, Ye X, Qiu W, et al. Risk factors for postoperative delirium in patients after coronary artery bypass grafting: A prospective cohort study. *J Crit Care*. 2015;30(3):606–12. <https://doi.org/10.1016/j.jcrc.2015.02.003>.
6. Marcantonio ER. Delirium in Hospitalized Older Adults. *N Engl J Med*. 2017;377(15):1456–66. <https://doi.org/10.1056/NEJMc1605501>.
7. Tse L, Schwarz SKW, Bowering JB, Moore RL, Barr AM. Incidence of and Risk Factors for Delirium After Cardiac Surgery at a Quaternary Care Center: A Retrospective Cohort Study. *J Cardiothorac Vasc Anesth*. 2015;29(6):1472–9. <https://doi.org/10.1053/j.jvca.2015.06.018>.
8. Igwe EO, Nealon J, Mohammed M, Hickey B, Chou K-R, Chen K-H, et al. Multi-disciplinary and pharmacological interventions to reduce post-operative delirium in elderly patients: A systematic review and meta-analysis. *J Clin Anesth*. 2020;67:110004. <https://doi.org/10.1016/j.jclinane.2020.110004>.
9. Cortés-Beringola A, Vicent L, Martín-Asenjo R, Puerto E, Domínguez-Pérez L, Maruri R, et al. Diagnosis, prevention, and management of delirium in the intensive cardiac care unit. *Am Heart J*. 2021;232:164–76. <https://doi.org/10.1016/j.ahj.2020.11.011>.

10. Fuchs S, Bode L, Ernst J, Marquetand J, Känel R von, Böttger S. Delirium in elderly patients: Prospective prevalence across hospital services. *Gen Hosp Psychiatry*. 2020;67:19–25. <https://doi.org/10.1016/j.genhosppsych.2020.08.010>.
11. Witlox J, Eurelings LSM, Jonghe JFM de, Kalisvaart KJ, Eikelenboom P, van Gool WA. Delirium in elderly patients and the risk of postdischarge mortality, institutionalization, and dementia: a meta-analysis. *JAMA*. 2010;304(4):443–51. <https://doi.org/10.1001/jama.2010.1013>.
12. Fong TG, Davis D, Growdon ME, Albuquerque A, Inouye SK. The interface between delirium and dementia in elderly adults. *Lancet Neurol*. 2015;14(8):823–32. [https://doi.org/10.1016/S1474-4422\(15\)00101-5](https://doi.org/10.1016/S1474-4422(15)00101-5).
13. Vasunilashorn SM, Fong TG, Albuquerque A, Marcantonio ER, Schmitt EM, Tommet D, et al. Delirium Severity Post-Surgery and its Relationship with Long-Term Cognitive Decline in a Cohort of Patients without Dementia. *J Alzheimers Dis*. 2018;61(1):347–58. <https://doi.org/10.3233/JAD-170288>.
14. Alifler M, Olsson B, Andreasson U, Cullen NC, Czyżewska J, Jakubów P, et al. Cardiac Surgery is Associated with Biomarker Evidence of Neuronal Damage. *J Alzheimers Dis*. 2020;74(4):1211–20. <https://doi.org/10.3233/JAD-191165>.
15. Evered L, Silbert B, Scott DA, Zetterberg H, Blennow K. Association of Changes in Plasma Neurofilament Light and Tau Levels With Anesthesia and Surgery: Results From the CAPACITY and ARCADIAN Studies. *JAMA Neurol*. 2018;75(5):542–7. <https://doi.org/10.1001/jamaneurol.2017.4913>.
16. DiMeglio M, Furey W, Hajj J, Lindekens J, Patel S, Acker M, et al. Observational study of long-term persistent elevation of neurodegeneration markers after cardiac surgery. *Sci Rep*. 2019;9(1):7177. <https://doi.org/10.1038/s41598-019-42351-2>.
17. Chan CK, Song Y, Greene R, Lindroth H, Khan S, Rios G, et al. Meta-analysis of ICU Delirium Biomarkers and Their Alignment With the NIA-AA Research Framework. *Am J Crit Care*. 2021;30(4):312–9. <https://doi.org/10.4037/ajcc2021771>.
18. Deiner S, Baxter MG, Mincer JS, Sano M, Hall J, Mohammed I, et al. Human plasma biomarker responses to inhalational general anaesthesia without surgery. *Br J Anaesth*. 2020;125(3):282–90. <https://doi.org/10.1016/j.bja.2020.04.085>.
19. Evered L, Silbert B, Scott DA, Ames D, Maruff P, Blennow K. Cerebrospinal Fluid Biomarker for Alzheimer Disease Predicts Postoperative Cognitive Dysfunction. *Anesthesiology*. 2016;124(2):353–61. <https://doi.org/10.1097/ALN.0000000000000953>.
20. Michels M, Michelon C, Damásio D, Vitali AM, Ritter C, Dal-Pizzol F. Biomarker Predictors of Delirium in Acutely Ill Patients: A Systematic Review. *J Geriatr Psychiatry Neurol*. 2019;32(3):119–36. <https://doi.org/10.1177/0891988719834346>.
21. Menzenbach J, Frede S, Petras J, Guttenthaler V, Kirfel A, Neumann C, et al. Perioperative Vascular Biomarker Profiling in Elective Surgery Patients Developing Postoperative Delirium: A Prospective Cohort Study. *Biomedicines* 2021;9(5). <https://doi.org/10.3390/biomedicines9050553>.

22. Chen Y, Lu S, Wu Y, Shen Y, Zhao H, Ding S, et al. Change in Serum Level of Interleukin 6 and Delirium After Coronary Artery Bypass Graft. *Am J Crit Care*. 2019;28(6):462–70.
<https://doi.org/10.4037/ajcc2019976>.
23. McKay TB, Rhee J, Colon K, Adelsberger K, Turco I, Mueller A, et al. Preliminary Study of Serum Biomarkers Associated With Delirium After Major Cardiac Surgery. *J Cardiothorac Vasc Anesth* 2021.
<https://doi.org/10.1053/j.jvca.2021.05.002>.
24. Fong TG, Vasunilashorn SM, Ngo L, Libermann TA, Dillon ST, Schmitt EM, et al. Association of Plasma Neurofilament Light with Postoperative Delirium. *Ann Neurol*. 2020;88(5):984–94.
<https://doi.org/10.1002/ana.25889>.
25. Middelorp J, Hol EM. GFAP in health and disease. *Prog Neurobiol*. 2011;93(3):421–43.
<https://doi.org/10.1016/j.pneurobio.2011.01.005>.
26. Oeckl P, Halbgebauer S, Anderl-Straub S, Steinacker P, Huss AM, Neugebauer H, et al. Glial Fibrillary Acidic Protein in Serum is Increased in Alzheimer's Disease and Correlates with Cognitive Impairment. *J Alzheimers Dis*. 2019;67(2):481–8. <https://doi.org/10.3233/JAD-180325>.
27. Verberk IMW, Thijssen E, Koelewijn J, Mauroo K, Vanbrabant J, Wilde A de et al. Combination of plasma amyloid beta(1–42/1–40) and glial fibrillary acidic protein strongly associates with cerebral amyloid pathology. *Alzheimers Res Ther* 2020;12(1):118. <https://doi.org/10.1186/s13195-020-00682-7>.
28. Elahi FM, Casaletto KB, La Joie R, Walters SM, Harvey D, Wolf A, et al. Plasma biomarkers of astrocytic and neuronal dysfunction in early- and late-onset Alzheimer's disease. *Alzheimers Dement*. 2020;16(4):681–95. <https://doi.org/10.1016/j.jalz.2019.09.004>.
29. Simrén J, Leuzy A, Karikari TK, Hye A, Benedet AL, Lantero-Rodriguez J, et al. The diagnostic and prognostic capabilities of plasma biomarkers in Alzheimer's disease. *Alzheimers Dement*. 2021;17(7):1145–56. <https://doi.org/10.1002/alz.12283>.
30. Jesse S, Steinacker P, Cepek L, Arnim CAF von, Tumani H, Lehnert S, et al. Glial fibrillary acidic protein and protein S-100B: different concentration pattern of glial proteins in cerebrospinal fluid of patients with Alzheimer's disease and Creutzfeldt-Jakob disease. *J Alzheimers Dis*. 2009;17(3):541–51.
<https://doi.org/10.3233/JAD-2009-1075>.
31. Lindroth H, Bratzke L, Twadell S, Rowley P, Kildow J, Danner M, et al. Predicting postoperative delirium severity in older adults: The role of surgical risk and executive function. *Int J Geriatr Psychiatry*. 2019;34(7):1018–28. <https://doi.org/10.1002/gps.5104>.
32. Sugimura Y, Sipahi NF, Mehdiani A, Petrov G, Awe M, Minol JP, et al. Risk and Consequences of Postoperative Delirium in Cardiac Surgery. *Thorac Cardiovasc Surg*. 2020;68(5):417–24.
<https://doi.org/10.1055/s-0040-1708046>.
33. Carrasco MP, Villarroel L, Andrade M, Calderón J, González M. Development and validation of a delirium predictive score in older people. *Age Ageing*. 2014;43(3):346–51.
<https://doi.org/10.1093/ageing/aft141>.

34. Sánchez-Cubillo I, Periañez JA, Adrover-Roig D, Rodríguez-Sánchez JM, Ríos-Lago M, Tirapu J, et al. Construct validity of the Trail Making Test: role of task-switching, working memory, inhibition/interference control, and visuomotor abilities. *J Int Neuropsychol Soc.* 2009;15(3):438–50. <https://doi.org/10.1017/S1355617709090626>.
35. Hsieh TT, Inouye SK, Oh ES. Delirium in the Elderly. *Clin Geriatr Med.* 2020;36(2):183–99. <https://doi.org/10.1016/j.cger.2019.11.001>.
36. Sánchez A, Thomas C, Deeken F, Wagner S, Klöppel S, Kentischer F, et al. Patient safety, cost-effectiveness, and quality of life: reduction of delirium risk and postoperative cognitive dysfunction after elective procedures in older adults-study protocol for a stepped-wedge cluster randomized trial (PAWEL Study). *Trials.* 2019;20(1):71. <https://doi.org/10.1186/s13063-018-3148-8>.
37. Wolters U, Wolf T, Stützer H, Schröder T. ASA classification and perioperative variables as predictors of postoperative outcome. *Br J Anaesth.* 1996;77(2):217–22. <https://doi.org/10.1093/bja/77.2.217>.
38. Rockwood K, Song X, MacKnight C, Bergman H, Hogan DB, McDowell I, et al. A global clinical measure of fitness and frailty in elderly people. *CMAJ.* 2005;173(5):489–95. <https://doi.org/10.1503/cmaj.050051>.
39. Baumberger D, Hunstein D. The linkage of nursing assessment and nursing workload. *Stud Health Technol Inform.* 2009;146:36–40.
40. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, et al. The Montreal Cognitive Assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc.* 2005;53(4):695–9. <https://doi.org/10.1111/j.1532-5415.2005.53221.x>.
41. Reitan RM. Validity of the Trail Making Test as an Indicator of Organic Brain Damage. *Percept Mot Skills.* 1958;8(3):271–6. <https://doi.org/10.2466/pms.1958.8.3.271>.
42. Rasmusson XD, Zonderman AB, Kawas C, Resnick SM. Effects of Age and Dementia on the Trail Making Test. *The Clinical Neuropsychologist.* 1998;12(2):169–78. <https://doi.org/10.1076/clin.12.2.169.2005>.
43. Lezak MD. *Neuropsychological assessment.* 5th ed. Oxford: Oxford University Press; 2012.
44. Inouye SK, van Dyck CH, Alessi CA, Balkin S, Siegel AP, Horwitz RI. Clarifying confusion: the confusion assessment method. A new method for detection of delirium. *Ann Intern Med.* 1990;113(12):941–8. <https://doi.org/10.7326/0003-4819-113-12-941>.
45. Inouye SK, Kosar CM, Tommet D, Schmitt EM, Puelle MR, Saczynski JS, et al. The CAM-S: development and validation of a new scoring system for delirium severity in 2 cohorts. *Ann Intern Med.* 2014;160(8):526–33. <https://doi.org/10.7326/M13-1927>.
46. Ely EW, Margolin R, Francis J, May L, Truman B, Dittus R, et al. Evaluation of delirium in critically ill patients: validation of the Confusion Assessment Method for the Intensive Care Unit (CAM-ICU). *Crit Care Med.* 2001;29(7):1370–9. <https://doi.org/10.1097/00003246-200107000-00012>.
47. Thomas C, Kreisel SH, Oster P, Driessen M, Arolt V, Inouye SK. Diagnosing delirium in older hospitalized adults with dementia: adapting the confusion assessment method to international

- classification of diseases, tenth revision, diagnostic criteria. *J Am Geriatr Soc.* 2012;60(8):1471–7. <https://doi.org/10.1111/j.1532-5415.2012.04066.x>.
48. Inouye SK, Leo-Summers L, Zhang Y, Bogardus ST, Leslie DL, Agostini JV. A chart-based method for identification of delirium: validation compared with interviewer ratings using the confusion assessment method. *J Am Geriatr Soc.* 2005;53(2):312–8. <https://doi.org/10.1111/j.1532-5415.2005.53120.x>.
 49. Diagnostic and Statistical Manual of Mental Disorders (DSM-5), Fifth Edition. Washington, DC: American Psychiatric Publishing, Inc; 2013.
 50. Wechsler D. WAIS-IV: Administration and scoring manual. San Antonio: Pearson; 2008.
 51. Wechsler D. WAIS-IV: Technical and interpretive manual. San Antonio: Pearson; 2008.
 52. Wechsler D. Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV). San Antonio: Pearson; 2008.
 53. Wechsler D. Wechsler Memory Scale-Fourth Edition (WMS-IV). San Antonio: Pearson; 2009.
 54. Wechsler D. WMS-IV: Technical and interpretive manual. San Antonio: Pearson; 2009.
 55. Welsh KA, Butters N, Mohs RC, Beekly D, Edland S, Fillenbaum G, et al. The Consortium to Establish a Registry for Alzheimer's Disease (CERAD). Part V. A normative study of the neuropsychological battery. *Neurology.* 1994;44(4):609–14. <https://doi.org/10.1212/wnl.44.4.609>.
 56. Rey A. L'examen psychologique dans les cas d'encephalopathie traumatique [Psychological examination in cases of traumatic encephalopathy]. 28th ed.: Archives de Psychologie; 1941.
 57. Osterrieth PA. Le test de copie d'une figure complexe; contribution à l'étude de la perception et de la mémoire [Test of copying a complex figure; contribution to the study of perception and memory]. Archives de Psychologie; 1944.
 58. Goldenberg G. Defective imitation of gestures in patients with damage in the left or right hemispheres. *J Neurol Neurosurg Psychiatry.* 1996;61(2):176–80. <https://doi.org/10.1136/jnnp.61.2.176>.
 59. Freedman M, Leach L, Kaplan E, Delis D, Shulman K, Winocur G. Clock-drawing: a Neuropsychological Analysis. New York: Oxford University Press; 1994.
 60. Goetz CG, Tilley BC, Shaftman SR, Stebbins GT, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): scale presentation and clinimetric testing results. *Mov Disord.* 2008;23(15):2129–70. <https://doi.org/10.1002/mds.22340>.
 61. Martinez-Martin P, Rodriguez-Blazquez C, Alvarez-Sanchez M, Arakaki T, Bergareche-Yarza A, Chade A, et al. Expanded and independent validation of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS). *J Neurol.* 2013;260(1):228–36. <https://doi.org/10.1007/s00415-012-6624-1>.
 62. Stiasny-Kolster K, Mayer G, Schäfer S, Möller JC, Heinzel-Gutenbrunner M, Oertel WH. The REM sleep behavior disorder screening questionnaire—a new diagnostic instrument. *Mov Disord.* 2007;22(16):2386–93. <https://doi.org/10.1002/mds.21740>.

63. Cummings JL, Mega M, Gray K, Rosenberg-Thompson S, Carusi DA, Gornbein J. The Neuropsychiatric Inventory: comprehensive assessment of psychopathology in dementia. *Neurology*. 1994;44(12):2308–14. <https://doi.org/10.1212/wnl.44.12.2308>.
64. Andreasen NC, Flaum M, Arndt S, Alliger R, Swayze VW. Positive and Negative Symptoms: Assessment and Validity. In: Marneros A, Andreasen NC, Tsuang MT, editors. *Negative Versus Positive Schizophrenia*. Berlin: Springer Berlin Heidelberg; 1991. pp. 28–51.
65. Klafki HW, Rieper P, Matzen A, Zampar S, Wirths O, Vogelgsang J, et al. Development and Technical Validation of an Immunoassay for the Detection of APP669-711 (A β -3-40) in Biological Samples. *Int J Mol Sci* 2020;21(18). <https://doi.org/10.3390/ijms21186564>.
66. Shahpasand-Kroner H, Klafki H-W, Bauer C, Schuchhardt J, Hüttenrauch M, Stazi M, et al. A two-step immunoassay for the simultaneous assessment of A β 38, A β 40 and A β 42 in human blood plasma supports the A β 42/A β 40 ratio as a promising biomarker candidate of Alzheimer's disease. *Alzheimers Res Ther*. 2018;10(1):121. <https://doi.org/10.1186/s13195-018-0448-x>.
67. Thijssen EH, La Joie R, Wolf A, Strom A, Wang P, Iaccarino L, et al. Diagnostic value of plasma phosphorylated tau181 in Alzheimer's disease and frontotemporal lobar degeneration. *Nat Med*. 2020;26(3):387–97. <https://doi.org/10.1038/s41591-020-0762-2>.
68. Karikari TK, Pascoal TA, Ashton NJ, Janelidze S, Benedet AL, Rodriguez JL, et al. Blood phosphorylated tau 181 as a biomarker for Alzheimer's disease: a diagnostic performance and prediction modelling study using data from four prospective cohorts. *Lancet Neurol*. 2020;19(5):422–33. [https://doi.org/10.1016/S1474-4422\(20\)30071-5](https://doi.org/10.1016/S1474-4422(20)30071-5).
69. Kuhle J, Regeniter A, Leppert D, Mehling M, Kappos L, Lindberg RLP, et al. A highly sensitive electrochemiluminescence immunoassay for the neurofilament heavy chain protein. *J Neuroimmunol*. 2010;220(1–2):114–9. <https://doi.org/10.1016/j.jneuroim.2010.01.004>.
70. Kuhle J, Barro C, Andreasson U, Derfuss T, Lindberg R, Sandelius Å, et al. Comparison of three analytical platforms for quantification of the neurofilament light chain in blood samples: ELISA, electrochemiluminescence immunoassay and Simoa. *Clin Chem Lab Med*. 2016;54(10):1655–61. <https://doi.org/10.1515/cclm-2015-1195>.
71. Ballweg T, White M, Parker M, Casey C, Bo A, Farahbakhsh Z, et al. Association between plasma tau and postoperative delirium incidence and severity: a prospective observational study. *Br J Anaesth*. 2021;126(2):458–66. <https://doi.org/10.1016/j.bja.2020.08.061>.
72. Casey CP, Lindroth H, Mohanty R, Farahbakhsh Z, Ballweg T, Twadell S, et al. Postoperative delirium is associated with increased plasma neurofilament light. *Brain*. 2020;143(1):47–54. <https://doi.org/10.1093/brain/awz354>.
73. Walter M, Wiltfang J, Vogelgsang J. Pre-Analytical Sampling and Storage Conditions of Amyloid- β Peptides in Venous and Capillary Blood. *J Alzheimers Dis*. 2020;78(2):529–35. <https://doi.org/10.3233/JAD-200777>.
74. Hu J, Feng X, Valdearcos M, Lutrin D, Uchida Y, Koliwad SK, et al. Interleukin-6 is both necessary and sufficient to produce perioperative neurocognitive disorder in mice. *Br J Anaesth*. 2018;120(3):537–

45. <https://doi.org/10.1016/j.bja.2017.11.096>.
75. Simone MJ, Tan ZS. The role of inflammation in the pathogenesis of delirium and dementia in older adults: a review. *CNS Neurosci Ther*. 2011;17(5):506–13. <https://doi.org/10.1111/j.1755-5949.2010.00173.x>.
76. Hesse R, Wahler A, Gummert P, Kirschmer S, Otto M, Tumani H, et al. Decreased IL-8 levels in CSF and serum of AD patients and negative correlation of MMSE and IL-1 β . *BMC Neurol*. 2016;16(1):185. <https://doi.org/10.1186/s12883-016-0707-z>.
77. McGrath ER, Himali JJ, Levy D, Conner SC, DeCarli C, Pase MP, et al. Growth Differentiation Factor 15 and NT-proBNP as Blood-Based Markers of Vascular Brain Injury and Dementia. *J Am Heart Assoc*. 2020;9(19):e014659. <https://doi.org/10.1161/JAHA.119.014659>.
78. Burton JK, Craig LE, Yong SQ, Siddiqi N, Teale EA, Woodhouse R, et al. Non-pharmacological interventions for preventing delirium in hospitalised non-ICU patients. *Cochrane Database Syst Rev*. 2021;7:CD013307. <https://doi.org/10.1002/14651858.CD013307.pub2>.

Tables

Table 1. Inclusion/exclusion criteria

Inclusion criteria
Patients of any gender
Age $\geq$ 50 years
Hospitalized in the Department of Cardiovascular and thoracic surgery for an elective cardiac surgery
Ability to speak, read and understand German
Signed informed consent
Exclusion criteria
Age < 50 years
Severe cognitive impairment (e.g. known dementia or inability to follow the assessment instructions)
Communication difficulties (e.g. severe hearing loss, aphasia)
Participation in another treatment trial likely to affect the outcomes of interest

Table 2. Visit schedule and assessments

Variables	t0	t1	t2	t3	t4	t5
	Pre-surgery	Post-surgery day 1-5	Post-surgery day 7	Post-surgery 3-5 m	Post-surgery 12 m	Post-surgery 18 m
Inclusion and exclusion criteria	X					
Clinical data and medical history	X				X	
Delirium screening questionnaire modified from PAWEL trial	X					
Frailty	X					
Hand grip strength	X					
Montreal Cognitive Assessment (MoCA)	X			X		X
Trail Making Test (TMTA and TMTB)	X			X		X
Laboratory measurements	X		X	X		X
ePA-AC	X					
Confusion Assessment Method (CAM-ICU/I-CAM)		X				
Chart review		X				
Neuropsychological Assessment				X		X
Additional neuropsychiatric diagnostic (if indicated)						
Movement Disorder Society -Unified Parkinson's Disease Rating Scale (MDS-UPDRS)				(X)		(X)
REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ)				(X)		(X)
Neuropsychiatric inventory (NPI)				(X)		(X)
Scale for the Assessment of Positive Symptoms (SAPS)				(X)		(X)

Table 3. Standard neuropsychological battery for assessment of cognitive domain according to DSM-5 criteria for neurocognitive disorders.

Cognitive domain	Tests	Function	References
Complex attention	Trail Making Test (TMTA)	A neuropsychological assessment as indicator of speed of cognitive processing and visuomotor tracking	[41]
	Coding (WAIS-IV)	A scale as indicator of processing speed for complex visual stimuli	[50–52]
Executive function	Trail Making Test (TMTB)	A neuropsychological assessment as indicator of set shifting ability, visuomotor tracking, divided attention, and cognitive flexibility	[41]
	Digit Span forward and backward (WAIS-IV)	A digit-span task is used to measure working memory's number storage capacity	[50–52]
Learning and memory	Logical Memory I and II (WMS-IV)	A scale for immediate und delayed verbal memory	[53,54]
	Visual Reproduction I and II (WMS-IV)	A subtest for immediate und delayed visual memory	[53,54]
	Word List learning, Recall and Recognition (CERAD)	A list of ten unrelated words is used for examining list learning, recall and recognition	[55]
	Constructional Praxis Recall (CERAD)	The test consists of a recall of the four figures from constructional praxis	[55]
Language	Semantic Fluency (CERAD)	The semantic (or category) fluency task consists of verbally naming as many words from a single category (animal) as possible in sixty seconds	[55]
	Letter Fluency (CERAD)	Letter fluency requires the generation of words from initial letter (S) In this study, 15 of the Boston Naming Test items are presented with five words each of low, medium	

	Boston Naming Test (CERAD)	and high frequency of occurrence	
Perceptual-motor function	Block Design (WAIS-IV)	A test for accessing constructional abilities	[50–52]
	Rey-Osterrieth Complex Figure Test	In this study we use only the copy part as indicator of visuospatial and constructional abilities	[56,57]
		This test of ideomotor apraxia asks for imitation of 10 finger gestures for both hands	[58]
	Imitation of finger gestures (Goldenberg)	The test asks for drawing copies of four geometrical figures	[55]
	Constructional Praxis (CERAD)	A test for assessment of visuoperceptual and visuospatial abilities, receptive language, numerical knowledge, working memory and executive functions	[59]
	Clock Drawing Test		

Table 4. Neuropsychiatric, sleep and motor symptoms will be assessed using established and standardized questionnaires and external rating scales, depending on the clinical presentation.

Questionnaire	Description	References
Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-UPDRS)	A comprehensive scale composed of four parts: Part I – Non-motor experiences of daily living (13 items); Part II Motor experiences of daily living (13 items); Part III Motor examination (18 items); Part IV – Motor complications (6 items). Each item scores from 0 to 4.	[60,61]
REM Sleep Behavior Disorder Screening Questionnaire (RBDSQ)	10-item screening tool for assessment of idiopathic REM sleep behavior disorder with short questions that have to be answered be either “yes” or “no”.	[62]
Neuropsychiatric inventory (NPI)	Comprehensive assessment of psychopathology in dementia measuring 10 behavioral disturbances: delusions, hallucinations, dysphoria, anxiety, agitation/aggression, euphoria, disinhibition, irritability/lability, apathy, and aberrant motor activity. Frequency and severity of each behavior are determined.	[63]
Scale for the Assessment of Positive Symptoms (SAPS)	34-item, 6-point scale measuring positive symptoms of schizophrenia with items listed under hallucinations, delusions, bizarre behaviors, and positive formal thought disorder.	[64]

Figures

Figure 1

Trial flow. MoCA Montreal Cognitive Assessment, TMTA Trail Making Test A, TMTB Trail Making Test, CAM Confusion Assessment Method, ICU intense care unit, IMC intermediate care unit

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Supplement1Deliriumscreeningquestionnaire20210621.docx](#)
- [Supplement2Medicalhistorysociodemography20210621.docx](#)
- [Supplement3ePAAC20210621.docx](#)
- [Supplement4ChartReview20210621.docx](#)