Prediction And Prevention of Postoperative Delirium In Older Patients

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List of abbreviations

ASA	American Society of Anesthesiologists
AUDIT	Alcohol Use Disorder Identification Test
AUDIT-C	Alcohol Use Disorder Identification Test-Consumption
AWS	Alcohol withdrawal syndrome
CCL2	CC-chemokine Ligand 2
CRP	C-reactive protein
DGAI	Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin
ESAIC	European Society of Anesthesiology and Intensive Care
EQ-5D-5L	EuroQol Visual Analog Scale
HbA1C	glycated hemoglobin value
HgB	Hemoglobin
hsTnT	Highly sensitive Troponine
ICD10	International Statistical Classification of Diseases and Related Health Problems (10^{th} revision)
MCP-1	Monocyte Chemoattractant Protein 1
mHELP	Modified Hospital Elder Life Program
MSS	Multi Sensory Stimulation
MoCA	Montreal Cognitive Assessment
NSAID	Nonsteroidal Anti-Inflammatory Drug
NT-pro-BNP	N-terminal Pro b-type Natriuretic Peptide
NYHA	New York Heart Association
POD	Postoperative Delirium
PROPDESC-study	PRe-Operative Prediction of postoperative DElirium by appropriate Screening study
PROPDESC-Val	PRe-Operative Prediction of postoperative DElirium by appropriate Screening-Validation
QoL	Quality of Life
SSQ	Single Sentence Question

1. Abstract

Introduction:

Postoperative delirium (POD) is a common and serious complication associated with increased morbidity, prolonged hospital stays, institutionalization, and elevated mortality rates. Early identification of patients at risk is essential, particularly in resource-constrained healthcare systems, to enable the timely implementation of targeted preventive interventions. Among others, age and alcohol drinking are predisposing factors for postoperative delirium (POD). Detailed patient data of the PROPDESC study (PRe-Operative Prediction of postoperative DElirium by appropriate SCreening) allows various ways to identify patients at risk for POD. Postoperative measures like early re-orientation, mobilisation or sleep routine, can be initiated to prevent POD after surgeries.

Methods:

This doctoral thesis consists of five publications of three different prospective clinical trials, covering the process of delirium prediction and delirium prevention in the perioperative process. Aiming to determine easy and accurate ways to identify patients at-risk at an early stage and prevent the occurrence of postoperative delirium. The use of a preoperative risk score is examined. Impact of preoperative blood values and alcohol consumption are evaluated. In the postoperative setting, a measure for delirium prevention in cardiac surgery patients was tested.

Results

Various preoperative routine blood values could be used together with the PROPDESC risk score to identify patients at risk for POD. The AUDIT-C is an accurate tool to assess the additional risk factor alcohol consumption. Postoperatively Snoezelen could reduce the incidence of POD in cardiosurgical patients significantly.

Conclusion

As POD is a severe, but often underrated adverse event, a synthesis of prediction through early identification and prevention via optimization of the perioperative process is needed to reduce the incidence of this event. The implementation of accurate prediction tools and suitable prevention measures in the perioperative routine could reduce the burden of this syndrome.

2. Introduction and aim with references

2.1. The burden of postoperative delirium

The continuously aging population and the increase in surgical procedures in older patients (53% of the surgeries conducted in 2020 were performed on patients over 60 years) already challenge the German healthcare system (statista).

Postoperative delirium (POD) is a post-surgical complication that can occur in patients of all ages, but higher age is a significant risk factor for POD (Mevorach et al. 2023a). It is often seen as a temporary impairment of brain function, often followed by complete remission, but occurrence of POD is also associated with increased morbidity and mortality (Salluh et al. 2015, Kotfis et al. 2018, Oh and Park 2019).

Individual risk factors are found to varying degrees in different age groups and influence the likelihood of incidence substantially. Risk factors for delirium can be categorised into two categories: predisposing factors are baseline characteristics, like the age or sex of the patient, comorbidities or pre-existing cognitive or sensory impairments. Some predisposing factors, for example age and surgical site, cannot be changed, while others like still influenceable cognitive or nutritional deficits could be subject to prehabilitation measures that aim to strengthen a patient´s resilience against the surgical impact. Prehabilitation measures to improve the above mentioned cognitive deficits could be, for example exercises to train attention, reaction time and memory (Jiang et al. 2024). Additionally, nutrition could be optimized to avoid dehydration or iron deficiency and vitamins or minerals could be prescribed in order to treat and improve nutritional deficits. Precipitating factors are defined as acute events or triggers that are related to the surgery (possible inflammatory reaction, length of procedure) and/or the accompanying anesthesiological procedure. They could contribute to the onset of POD in already vulnerable patients and they are potentially modifiable.

As mentioned in the 2017 published guideline of the European Society of Anaesthesiology and Intensive Care (ESAIC), there are many different predisposing parameters ranging from the patient´s preoperative medication to his childhood education, including cognitive impairment, comorbidities, sensory deficits (visual impairment, hearing impairment), pre-operative habit of alcohol consumption, poly-medication, impaired functional status

(immobility), and frailty (Inouye et al. 2014a, Aldecoa et al. 2017, Marcantonio 2017). Other studies found higher age, hypoalbuminemia, or dementia significantly associated with POD (Robinson et al. 2009). The kind of comorbidities contributing to the development of POD range from urinary tract infection or pneumonia, dehydration, electrolyte abnormalities, acute kidney injury or liver failure, ethanol or benzodiazepine withdrawal, central nervous system insults, seizures, congestive heart failure to acute myocardial infarction (Vasilevskis et al. 2012). Mechanisms involved in the development of POD, such as neurotransmitters, inflammation, physiological stressors, metabolic disorders, electrolyte imbalances and genetic factors, can also occur in younger people (Inouye et al. 2014a).

Potentially modifiable, precipitating factors for POD are perioperative drugs (especially sedative hypnotic agents and anticholinergic agents), the kind of surgery (e.g. the surgical stress or duration of the procedure, the blood loss), anaesthesia, high pain levels, anemia, infections, acute illness, acute exacerbation of chronic illness, the use of physical restraints, and electrolyte disturbances (Inouye et al. 2014a, Marcantonio 2017). Other precipitating factors are addition of more than three medications, use of bladder catheter, and any iatrogenic event (Inouye and Charpentier 1996). The sum of predisposing and precipitating factors determine the patient´s risk for POD (Inouye and Charpentier 1996).

Despite the potential serious harm for patients and the burden on healthcare resources (both monetary and organisational) caused by POD, there is currently no standardised risk screening in German hospitals (Bickel et al. 2008, Inouye et al. 2014a, Weinrebe et al. 2016, Kirfel et al. 2021) even though this is recommended in the ESAIC evidence-based and consensus-based Guideline on Postoperative Delirium (Aldecoa et al. 2017). A S3 Guideline with participation of the DGAI (Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin) was planned to be completed in April 2025, but is not published yet. Its aim is to provide interdisciplinary and interprofessional guidance on delirium prevention, diagnosis and treatment in older adults with a focus on non-substance-related delirium outside the intensive care setting. This guideline particularly considers primary and secondary delirium prevention, as well as diagnosis and management with pharmacological and non-pharmacological measures (AWMF Leitlinienregister 2021) and complements the actual S3 Guideline for Analgesia, sedation, and delirium management in intensive care medicine that was updated in August 2025.

2.2 Pre-operative prediction of postoperative delirium

In the past there have been some attempts to create risk prediction models for postoperative delirium that included different risk factors. Thus far, externally validated models require extensive cognitive testing, functional assessments or laboratory values, and partly include further scores or data not available regularly prior to surgery (Lindroth et al. 2018). Van Meenen et al. found 37 models with sensitivity ranging from 0.25 to 0.81 and specificities from 0.49 to 0.96, but she concluded that the current evidence was too weak to recommend one of the models for clinical practise (van Meenen et al. 2014). Another fact that limited the practicability of the existing scores was that some of the relevant predictors were specific to a particular patient group (e.g. cardiac patients) or that preoperative assessment tools were too time consuming (van Meenen et al. 2014, Lindroth et al. 2018). Additionally, there have been attempts to develop a pre-operative prediction score for POD by Inouye et al. (Inouye et al. 1993) and Kim et al. (Kim et al. 2016, 2020), but these scores use parameters that are not generally available on the premedication visit.

The aim of the PROPDESC study was to generate a universal pragmatic score based on preoperative data from patients of various surgical disciplines, which is easily applicable and thus can be implemented in clinical routine for preoperative POD risk screening. The PROPDESC study was conducted at the University Hospital Bonn in 2018 and 2019 to develop an easy to administer screening tool for patients at risk for POD after their planned elective surgery (Menzenbach et al. 2019). The PROPDESC score combines the patient´s age, the ASA score (American Society of Anaesthesiology score), the NYHA score (New York Heart Association score), the 3-level modified Johns Hopkins surgical criteria (Donati et al. 2004), and two questions of the MoCA (Montreal Cognitive Assessment) to an easy to calculate score (Menzenbach et al. 2022).

In the cause of the PROPDESC study a routine blood sample is taken from all planned surgical patients at their pre-hospital admission visit to the University Hospital Bonn for screening purposes. A variety of pre-operative available blood parameters have been analysed to find or confirm a possible relationship to the occurrence of POD.

Those parameters focus on mechanisms and structures such as neurotransmitters, inflammation, physiological stressors, metabolic disorders, and electrolyte imbalances. A sub-study of the PROPDESC study that analyzed 17 serum biomarkers specific for

vascular activation and permeability as well as for inflammation found that surgery-induced systemic inflammation, evidenced by an increase of CCL2 (CC-chemokine Ligand 2), also referred to as MCP-1 (Monocyte Chemoattractant Protein 1) was associated with POD in patient that underwent cardiac surgery (Menzenbach et al. 2021). Deranged concentrations of these factors can also occur in younger people (Inouye et al. 2014a, Menzenbach et al. 2021).

POD is accompanied by postoperatively raised values of C-reactive protein (CRP) and Interleucin-6 (Liu et al. 2020). Therefore, C-reactive protein (CRP) is a candidate for a possible pathophysiological mechanism of POD that includes neuroinflammation (Jin et al. 2020). Among others, neuroinflammation induces changes of the synaptic plasticity, that might explain cognitive dysfunction during episodes of postoperative delirium (Prieto et al. 2019). HbA1C (glycated hemoglobin value) is an indicator for re-occurring or persisting hyper-glycaemia; that is known for enhancing inflammation and oxidative stress (Dandona et al. 2007, Hyun et al. 2011). Additionally, pre-operative anemia could lead to a cognitive dysfunction postoperatively (Raats et al. 2015) and metabolic derangements and dehydration were found as predisposing and precipitating risk factors for POD (Hoogma et al. 2023). A possible influence of hypo- and hypernatremia on the development of POD has still to be clarified, as some studies found a positive correlation of sodium levels with POD (Galanakis et al. 2001, Zhang et al. 2020) whereas others found no relationship (Smulter et al. 2013, Scholz et al. 2016). A review published in 2023 identified - among many other factors - anemia, infections, malnutrition, metabolic derangements, and dehydration as predisposing and precipitating risk factors for POD (Hoogma et al. 2023). Another review found low hematocrit; low hemoglobin, low serum albumin and potassium levels; increased values of creatinine, (CRP), and white blood cell count; and low as well as increased serum sodium again among other variables to be potentially representative of a POD risk profile (Mevorach et al. 2023b).

Furthermore, a correlation of the cardiac biomarkers troponin (hsTnT) and N-terminal pro b-type natriuretic peptide (NT-pro-BNP) with increased POD risk was observed. This might be explained by the association triggers of delirium such as impaired cerebral perfusion (Yokota et al. 2003, Fong et al. 2006), systemic inflammation (Athilingam et al. 2013) or cardio-embolic events (de la Torre 2012).

2.3 Detection of patients at risk through appropriate screening tools

As resources are limited in an already stretched healthcare system, personnel- and cost-intensive efforts to prevent POD should be directed to patients at increased risk. Therefore, routine screening for POD risk prior to surgery is essential and recommended by guidelines on postoperative delirium (Reilly and Evans 2006, Aldecoa et al. 2017).

The PROPDESC-study included data of older patients (≥60 years) from various surgical disciplines. It showed a good prediction accuracy and could be done in a short time. This promising universal risk screening tool is currently externally validated in the PROPDESC-Val study (PRe-Operative Prediction of postoperative DElirium by appropriate Screening-Validation) (Guttenthaler et al. 2024). Complementing the PROPDESC score it might be useful to pre-operatively screen for a patient´s alcohol consumption level as high alcohol consumption is a risk factor for POD (Wu et al. 2023) and older patients with a high drinking level are especially at risk (Vijayakumar et al. 2014).

In the PROPDESC patient sample alcohol consumption was not significantly associated with the occurrence of POD. This result is consistent with the finding of Eliasen et al. (Eliasen et al. 2013). Her large review found no significant association between alcohol consumption and neurological complications, but she found evidence of heterogeneity between the studies (Eliasen et al. 2013). One reason for the negative association between alcohol consumption and POD in the PROPDESC study could be that response behaviour could be influenced by a variety of social context or environmental factors including the assessment setting and the immediate interpersonal situation, which may involve research staff (Del Boca and Darkes 2003). In the PROPDESC study older patients were asked by medicinal students in a face-to-face interview about their drinking habits. A setting that is likely to create a response bias as it has to be considered, that the motivation to put across a good impression has a significant impact on self-report of alcohol consumption (Davis et al. 2010). At last one has to bear in mind, that the aim of the PROPDESC study was the evaluation of a pre-operative risk score for postoperative delirium and that the data derived during conduction lacks the inclusion of some potentially relevant confounding variables, for example the social status of the patient as well as additional addiction habits like smoking, that could also enhance the subjective quality of life (Poikolainen et al. 1996). Another reason could be the fact that there were only very few patients in the PROPDESC

study that consumed alcohol excessively according to the AUDIT-C and as the question about daily alcohol consumption only asked about the frequency but not the quantity of alcohol consumption, it was not suitable to detect excessive alcohol intake. These circumstances might have led to the lack of significance of alcohol consumption on the occurrence of POD in the PROPDESC patient sample.

Beside a raised risk for POD individuals with excessive alcohol consumption could develop an alcohol withdrawal symptom (AWS) during their hospital stay which could additionally pose significant life-threatening dangers (Vagts and Nöldge-Schomburg 2002, Vagts et al. 2003). Eliasen et al. found that excessive alcohol intake was also linked to a heightened risk of postoperative mortality (Eliasen et al. 2013). The underlying causes of an increased perioperative risk for high level alcohol drinkers likely involve multiple factors, such as dysfunction of various organ systems induced by alcohol before surgery, an amplified response to surgical stress, and/or dysfunctions triggered by abstinence (Tønnesen and Kehlet 1999).

A nationwide representative survey of 18- to 64-year-old German citizens that used the AUDIT (Alcohol Use Disorder Identification Test) as assessment tool revealed that 70.5% had consumed alcohol in the past 30 days with problematic alcohol consumption (defined as exceeding an average daily consumption of pure alcohol of 12 grams for women or 24 grams for men) being present in 17.6% of respondents (Rauschert et al. 2022).

2.4. Initiation of preventive measures before the surgical procedure

To be able to initiate measures for POD prevention early enough it is important to detect patients at risk as early as possible in the clinical setting. This could, for example, be done with the help of the PROPDESC score. Preventive measures like avoidance of pre-operative polypharmacy, adequate pre-operative pain management and comprehensive geriatric assessment can help to prevent occurrence of POD (Jin et al. 2020).

The routine laboratory values of patients with a high risk for POD according to the PROPDESC score could be additionally screened for potentially POD enhancing conditions. For male patients for example, pre-operative anemia with Hb < 13 g/dl is a significant risk factor for POD (Hoogma et al. 2023). This condition could be detected and preoperative measures like Iron or Vitamin B12 supplementation, depending on the

underlying cause for the deficiency, could be initiated before the upcoming surgical procedure. These include long-term glycaemic control of diabetic patients, reducing increased inflammatory activity, and correcting hypernatremia or anemia. Radke et al. discovered prolonged fasting time without fluid intake > 6 h as an independent risk factor for the development of POD (Radtke et al. 2010) whereas Scholz et al. and Smulter et al. did not see abnormal preoperative electrolyte levels as risk factors for POD (Smulter et al. 2013, Scholz et al. 2016). Other studies found preoperative hypo- or hypernatremia as significant risk factors (Galanakis et al. 2001, Zhang et al. 2020, Mevorach et al. 2023b).

Beside abnormal laboratory parameters, there are other conditions that could enhance the risk of POD occurrence. One is an alcohol use disorder. Correct knowledge of a patient´s alcohol consumption is important in the clinical setting for several reasons. It provides the treating physicians with the opportunity to initiate preventive measures against alcohol-induced perioperative complications and it indicates the vulnerability of the patient for POD onset. Additionally, patients with a known high level of alcohol intake could be encouraged to reduce their alcohol consumption preoperatively in order to reduce their risk for POD. Initiated early enough alcohol reduction could lead to a better postoperative outcome by improving several organic dysfunctions and in consequence reducing postoperative morbidity (Tønnesen 2003). Discontinuation of alcohol consumption four to eight weeks prior to any surgical procedure could potentially decrease the incidence of postoperative complications (Egholm et al. 2018).

In the immediate clinical setting the early and accurate detection of patients with alcohol drinking problems can help to avoid the occurrence of an alcohol withdrawal syndrome (Ungur et al. 2020). Therefore, accurate screening tools are important.

A sub-analysis of the PROPDESC-study evaluated the alcohol consumption of older patients with two different assessment tools (single sentence question and Alcohol Use Disorder Identification Test-Consumption (AUDIT-C)) and compared the results in regards to detection, reliability, and quantification of patient´s alcohol consumption.

2.5. Intra-and postoperative measures to minimize POD risk in older patients

Intraoperative measures to prevent POD are for example, the monitoring of anaesthesia depth (Evered et al. 2021) the use of multimodal opioid-sparing analgesia (Weinstein et al.

2018) and the use of paracetamol and/or NSAIDs (Memtsoudis et al. 2019), intraoperative and postoperative dexmedetomidine administration (Deiner et al. 2017) or the reduction of surgical trauma by using minimal invasive techniques (Jin et al. 2020). There are numerous medications that may increase the risk of postoperative delirium, including tricyclic antidepressants and certain antihistamines (Jin et al. 2020). In the perioperative period, some studies found the most relevant medications to be benzodiazepines (Weinstein et al. 2018, Memtsoudis et al. 2019), sometimes used as a premedication for anxiolysis, whereas the i-PROMOTE study could not confirm those findings (Kowark et al. 2024). In the latter study this could be due to the low dose or the administration route of midazolam or the composition of the patient sample, that excluded patients with high prevalence for POD like cardiosurgical patients. Other relevant medications that could enhance the occurrence of POD are gabapentinoids, and scopolamine (Jin et al. 2020).

Intraoperatively avoidance of hypothermia and blood transfusions could also reduce the POD risk (Jin et al. 2020).

Postoperatively non-pharmacological methods are the first-line preventative interventions for POD. Reorientation to help patients get familiarised with the environment, reduction of staff change and patient transfer, access to natural light and time-keeping devices are some examples (Jin et al. 2020).

A pharmacological preventive treatment could be perioperative melatonin administration (Campbell et al. 2019).

A non-pharmacological method preventing POD could be the Multisensory stimulation (MSS) so called Snoezelen. Snoezelen was first introduced in the 1970s as an intervention for people with learning disabilities, based on the rationale of reducing the adverse effects of sensory deprivation. Over the time this application has been extended to the care of older people with dementia as both groups share some common characteristics such as reduced cognitive functions and diminished communicative ability (Chung et al. 2002).

It creates gentle stimulations and a relaxing atmosphere that helps to reduce agitation and anxiety. Other studies used music or bright light therapy, some of them used training of healthcare professionals on delirium awareness as intervention (Inouye et al. 1999, 2014b,

Marcantonio et al. 2001, McCaffrey and Locsin 2004, Lundström et al. 2005, Caplan and Harper 2007, McCaffrey 2009, Chen et al. 2011, Ono et al. 2011, Hshieh et al. 2015).

The characteristics of the Snoezelen are: a) visual, auditory, tactile, and olfactory stimulation in a room or environment using lights, music, aromas, and tactile objects; b) individual and non- directive intervention in which participants choose the sensory stimuli; c) use of non-sequential stimulus (a sensory input or event that occurs without a predictable order or pattern) and non-standardized stimulus (a stimulus that is not consistently applied or controlled) ; d) reduced cognitive requirements (Baker et al. 2001). In the monocentric, prospective, randomized, controlled, non-pharmacological interventional Feel Well study 237 patients older than 65 years that underwent elective cardiac surgery at the University Hospital Bonn from September 2021 until July 2022 were included (Dogan et al. 2023). The intervention group received postoperative MSS treatment for three consecutive postoperative days 20-minutes per day. In this study, In patients receiving MSS intervention after elective cardiac surgery incidence of POD was reduced by 54.4 % (Dogan et al. 2023).

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RESEARCH Open Access

Preoperative evaluation of alcohol consumption in older patients

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Abstract

Purpose This sub-analysis of the PROPDESC-study (Pre-Operative Prediction of postoperative delirium by appropriate Screening-study) evaluated the alcohol consumption of older patients with two different assessment tools (single sentence question and Alcohol Use Disorder Identification Test-Consumption (AUDIT-C)) and compared the results in regards to detection, reliability, and quantification of patient´s alcohol consumption.

Methods During their anesthesiological pre-clinic visit 1084 patients older than 59 years were asked whether they consume alcohol daily and 668 of them additionally answered the AUDIT-C questionnaire.

Results According to the SSQ 11.72% of the patients consumed alcohol daily. In the AUDIT-C sub-group 25.90% reported moderate to high alcohol consumption while infrequent or very low alcohol intake was reported by 41.92%. In the subgroup 31.89% of the patients stated alcohol abstinence. About one quarter (25.13%) of patients who denied daily alcohol intake but scored positive on the AUDIT-C displayed levels of alcohol consumption ranging from moderate (11.20%) to high (13.87%) according to the AUDIT-C.

Conclusion Reliable information about alcohol consumption is related to the method of questioning. The AUDIT-C evaluates the patient´s alcohol intake precisely and identifies more older patients with possibly health- and surgery-relevant alcohol consumption levels. The validated AUDIT-C provides an objective assessment to the physician during the pre-clinic anesthesiologic consultation. Additionally, handing out a questionnaire to the patient encourages initiative and self-assessment and could also relieve both, the physician and the patient from sensing a moral evaluation of alcohol consumption.

Keywords Alcohol consumption, AUDIT-C, Anesthesiological evaluation, Preoperative alcohol assessment

Introduction

According to the 2024 World Health Organization (WHO) Report on alcohol consumption the level of "per capita alcohol consumption" (APC) in the European Union (EU) is still the highest in the world [1]. A nationwide representative survey of 18- to 64-year-old German citizens that used the AUDIT (Alcohol Use Disorder Identification Test) as assessment tool revealed that 70.5% had consumed alcohol in the past 30 days [2] with episodes of binge drinking being more often reported by men (41.9%) than by women (23.3%) [2]. Problematic alcohol consumption (defined as exceeding an average daily consumption of pure alcohol of 12 g for women or 24 g for men) was present in 17.6% of respondents [2].

Therefore, patients who are scheduled for elective surgery in a German hospital have a reasonable high possibility to present with a history of alcohol consumption.

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In individuals with excessive alcohol consumption, the manifestation of alcohol withdrawal symptoms during their hospital stay could pose significant life-threatening dangers [3, 4]. These risks stem on one hand from interactions between medications as well as direct pharmacological interactions between alcohol and narcotics and on the other hand from physiological alterations [3, 4]. Therefore, it is crucial to detect patients at risk for alcohol withdrawal syndrome (AWS) as early as possible in order to treat them with the appropriate prophylactic medication [5].

The underlying causes of a heightened perioperative risk for high level alcohol drinkers likely involve multiple factors, such as dysfunction of various organ systems induced by alcohol before surgery, an amplified response to surgical stress, and/or dysfunctions triggered by abstinence [6]. Research on pathophysiological mechanisms indicates that excessive alcohol intake diminishes immune function, heightens the endocrine stress response to surgery, and retards the wound healing process [7]. In total joint arthroplasty the amount of alcohol intake of male patients could influence the number of postoperative complications [8] and male patients diagnosed as chronic alcohol drinkers that had to undergo major tumor surgery had an increased risk for mortality and morbidity after surgery [9].

A meta-analysis by Eliasen et al. revealed that preoperative alcohol consumption correlates with heightened risks of a variety of postoperative complications, encompassing general morbidity, wound healing problems, pulmonary complications, prolonged hospital stay, and intensive care unit admission [10]. The same review found no association between low to moderate alcohol consumption and general morbidity and infections, wound intricacies, and cardiopulmonary or neurological complications [10]. Eliasen et al. additionally conducted a sub-analysis to evaluate the impact of high alcohol consumption and their findings indicated that excessive alcohol intake was also linked to a heightened risk of postoperative mortality [10]. The nature of the surgical procedure did not appear to affect the relationship between alcohol consumption and postoperative complications [10]. Rubinsky et al. evaluated that surgical patients with very high AUDIT-C scores (9–12 points) stayed longer on ICU (intensive care unit) and in hospital, and had an increased risk of return to the operating room within 30 days after their surgery compared to the low-risk drinking patients (AUDIT-C scores 1–4) [11].

To be able to estimate a possible risk of alcohol-induced perioperative complications provides the opportunity to initiate measures in a timely manner. Therefore, reliable estimation of a patient´s alcohol consumption is of high importance for the attending physicians.

However, patients seem to expect discussions about their alcohol consumption more during appointments or routine check-ups than during consultations for non-alcohol-related issues [12]. Another barrier to effective screening before a surgical intervention could be insufficient management of staff workload or a reluctance of the professional to ask patients about alcohol drinking without clear signs of risky drinking behavior [12]. Avoidance of questions about alcohol consumption levels could be related to the fact, that some professionals had encountered negative reactions from the respondent in terms of embarrassment and unease, which emphasizes that a good rapport between patient and professional is helpful in discussing sensitive topics such as drinking behavior [12].

The U.S. Preventive Service Task Force (ASPSTF) recommends using the NIAAA (National Institute on Alcohol Abuse and Alcoholism) Single Alcohol Screening Question (SASQ) or the AUDIT-C as quick and effective screening tools [13]. The SASQ is part of a two-step screening process. Initially, participants are asked about their occasional consumption of alcoholic beverages, and only those who respond affirmatively are asked the subsequent screening question: "How many times in the past year have you had X or more drinks in a day?" (where "X is 5 for men and 4 for women, and a response of >1 is considered positive") [13] In 2009, Smith et al. conducted a trial with 286 subjects, the majority of them identifying themselves as black or African-American [14]. He compared the two steps screening process mentioned above with the AUDIT-C and evaluated that this face-to-face questioning demonstrated comparable sensitivity and specificity in identifying unhealthy alcohol use among his sample of primary care patients compared to the AUDIT-C [14]. The AUDIT-C itself has been validated in various settings and cohorts. Bradly et al. found in a study with adult outpatients at an academic family practice clinic that the AUDIT-C performed as well as the full AUDIT and significantly better than self-reported risky drinking [15]. Bush et al. interviewed 393 male general medical patients and found the questions of the AUDIT-C to be a practical, valid primary care screening test for heavy drinking and/or dependence [16].

The objective of this sub-analysis was to assess the reliability of a SSQ (Single sentence question) administered in a pre-clinical context compared to the outcomes obtained from the Alcohol Use Disorders Identification Test Consumption questions (AUDIT-C) concerning the identification and measurement of preoperative alcohol intake.

Methods

Results of this analysis are derived out of the PROPDESC-study (Pre-operative prediction of postoperative delirium by appropriate screening-study) that was designed and conducted as an prospective, observational, mono-centric study to create an easy pre-operative score to detect patients at risk for postoperative delirium [17, 18]. Inclusion criteria for the PROPDESC study were age of 60 years or older, a planned surgical intervention of more than 60 min, and written informed consent. Patients undergoing emergency procedures, patients with difficulties in the German language or pre-existing mental retardation or severe dementia that might complicate cognitive testing and delirium assessment were excluded. Laboratory values that have been recognized as possible predictive values for the occurrence of POD (postoperative delirium) were assessed in the cause of pre-clinic routine laboratory blood examination [17]. Since heavy alcohol intake was recognized as a risk factor for postoperative delirium [19], all participants were questioned about their daily alcohol consumption habits by trained study personnel during their visit to the anesthesiological pre-admission clinic. Further details of the PROPDESC study can be found in the publication of the study protocol [17].

After the inclusion of 429 patients, an amendment was made to the study, that added the conduction of the AUDIT-C. The AUDIT-C questionnaire comprises the first three questions of the AUDIT [20]. The first question asks about the frequency of consuming alcoholic beverages. The second question inquires the typical number of standard drinks consumed per day. The third question focuses on the frequency of consuming six or more drinks on a single occasion [20]. As mentioned above the AUDIT-C was validated in various settings as a screening tool for heavy alcohol consumption.

Answers to the AUDIT-C are rated 0–4 points, adding up to a maximum of 12 points. In our analysis four groups of consumption levels were distinguished: no consumption/abstinence (0 points), low or infrequent (1–3 points), moderate (4 points), and high (AUDIT-C score > 4) alcohol consumption in the year before the questioning. These groups were formed under the consideration that the cut-off value for heavy alcohol consumption has to be adjusted to the age to achieve reasonable sensitivity and specificity of the results. Aalto et al. found that a cut-off of > = 4 led to a sensitivity of 0.94 and a specificity of 0.80 for the detection of heavy drinking in a stratified random sample of 804 Finns aged 65–74 years [21]. The AUDIT has been translated into many languages. All translations are available online [22]. In this setting the German version of the AUDIT-C version recommended by the German Medical Association (Bundesärztekammer, Suchtforschungsverbund Baden-Württemberg, UKL Freiburg) was used [23]. This version defined one glass of alcohol as the equivalent of 0.33 L beer, 0.25 L wine of sparkling wine or 0.02 L of liquor. After approval of the protocol amendment study patients were additionally asked the AUDIT-C regardless of the answer given to the SSQ question. All study related procedures were conducted by trained study personnel.

Statistics: Answers to the questions about alcohol consumption were evaluated in the complete patient group and for female and male patients separately. The level of alcohol consumption in relation to age was examined by dividing the AUDIT-C groups in subgroups spanning 10-year increments. Alcohol consumption was analyzed in the total patient group and in the group of patients that additionally answered the AUDIT-C questionnaire. Statistical analysis was performed using the statistical programming environment R. For the description of the cohorts, continuous and ordinal variables are presented with mean and ± standard deviation (sd). Nominal variables are reported as numbers and percentages. Laboratory values are presented with median and interquartile range (IQR), due to the inherent skewness. The differences between the cohorts were analyzed using the nonparametric Wilcoxon rank sum test for continuous variables (no normal distribution was present) and Fisher's exact test for categorical variables, using a two-sided significance level of 0.05.

Results

Of the 1097 included patients seven patients were excluded due to missing answers to the SSQ. Additionally, four patients were excluded, because they withdrew their informed consent to the PROPDESC study and two patients were excluded due to inconsistent data (Fig. 1).

Therefore, 1084 patients that answered the SSQ were analyzed; 425 (39.28%) of them were women. Patients had a mean age of 72.42 years (Table 1). The patient sample included 668 patients that additionally answered the AUDIT-C. Of all included patients 957 (88.28%) answered the SSQ in the negative and 127 (11.72%) confirmed daily alcohol (Table 1). The characteristics of the patients that answered the SSQ negative differed not significantly from the daily drinkers in regards to their age, ASA (American Society of Anesthesiologists) class and NYHA (New York Heart Association) classification, their planned surgical category, and their revised cardiac risk index (rCRI). Daily drinking patients differed in some aspects significantly from patients that negated daily alcohol intake. In the group confirming daily alcohol consumption were significantly more men ($p < 0.001$), patients had a significantly higher education ($p < 0.001$), and scored significantly higher on the MoCA (Montreal Cognitive assessment) test ($p = 0.017$) (Table 1). They also had significantly higher gamma-GT (gamma glutamyl

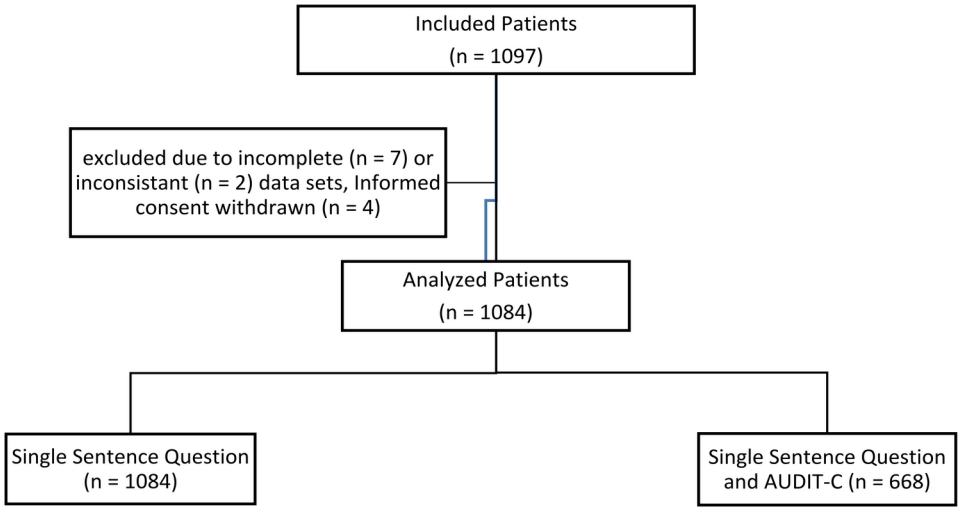

Fig. 1 Modified after Menzenbach et al. [18]

transpeptidase) laboratory values ($p < 0.001$) and hemoglobin values ($p = 0.036$), but it has to be noted that many laboratory values are missing as they were not assessed routinely at the pre-admission visit (Table 1).

To the SSQ question 668 patients additionally answered the AUDIT-C. Of those patients 173 (total 25.90%, with 21.71% men and 4.19% women) scored more than 3 points on the AUDIT-C indicating moderate to high alcohol consumption. Table 2 shows the characteristics of the AUDIT-C group and the subgroups comprised of patients who scored 0–3 points and patients with more than 3 points on the AUDIT-C. Patients in the higher consumption group were significantly younger ($p = 0.008$), had a higher education ($p = 0.003$), and scored better on the MoCA test (Montreal Cognitive Assessment) than patients with an AUDIT-C result below 4 points. The differences in the laboratory values matches those of the SSQ group. Patients with AUDIT-C results above the Cut-off had significantly higher gamma-GT values ($p = 0.014$) and significantly higher hemoglobin values ($p = 0.003$) (Table 2).

Of all 375 patients that answered the SSQ in the negative 56.05% scored ≥ 1 point on the AUDIT-C (Table 3). Most of them reached a maximum of 3 points on the AUDIT-C (74.87%, Table 3), but 94 (25.13%) scored more than 3 points on the AUDIT-C (Table 3). Of those patients 11.23% reported moderate alcohol intake (AUDIT-C = 4), and 13.90% scored 5 points or more, indicating frequent or high alcohol consumption (Table 3). In total, one quarter (25.13%) of the patients who denied daily alcohol consumption on the SSQ but scored positive on the AUDIT-C reached more than 3 points indicating moderate to high alcohol intake.

Of 83 patients that answered the SSQ in the affirmative four scored 0 points on the AUDIT-C. The characteristics of those four patients are displayed in Table 4. We compared this small group of patients to the other patients that answered the SSQ in the positive, but the differences were not significant with the exception of the creatinine value that was higher in the four patients with contradicting answers (Table 4). It has to be mentioned that this small group had a lower mean MoCA test result than that of all other groups.

According to the SSQ 127 patients (11.72%) drank alcohol daily. The percentage of patients consuming alcohol daily decreased with increasing age (Supplemental Material Table 1) and the percentage of daily drinkers was higher among men in all age groups (Supplemental Material Table 2).

Of all patients, that answered the AUDIT-C questionnaire, 32.04% scored 0 points indicating alcohol abstinence in the year before their elective surgery (Supplemental Material Table 2). Infrequent or low alcohol intake (AUDIT-C score of 1–3 points) was reported by 42.07% of the patients, while 25.90% reported a moderate to high alcohol consumption (4–12 points) (Supplemental Material Table 2).

Discussion

This sub-analysis within the PROPDESC study aimed to evaluate the comparative reliability of two short methods to assess preoperative alcohol consumption among older surgical patients as an early, time-saving, and accurate detection of patients with AUD (Alcohol use disorder) is very important in a clinical setting. Important aspects for acceptance of a screening tool for alcohol consumption in the daily clinical setting beside its easy administration are difficulty, extensiveness, and suitability for self-completion. Assessment of a patient´s alcohol consumption level should be as early before surgery as possible, as this provides the opportunity to encourage preoperative alcohol reduction. Initiated early enough alcohol reduction

Table 1 Comparison of all patients in regards to their answer to the SSQ

	All patients	SSQ negativ	SSQ positiv	*p*-value	missings
N (%)	1084 (100.00)	957(88.28)	127 (11.72)		
Age(mean ± sd)	72.42 (± 7.4)	72.53 (± 7.35)	71.65 (± 7.76)	0.164	0
Sex				< 0.001*	2
Female, n (%)	425	403 (42.11)	22 (17.32)		
Male, n (%)	657	552 (57.68)	105 (82.69)		
ASA, n (%)				0.634	9
1	26	23 (2.4)	3 (2.36)		
2	364	318 (33.23)	46 (36.22)		
3	600	530 (55.38)	70 (55.12)		
4	84	78 (8.15)	6 (4.72)		
5	1	1 (0.1)	0		
Surgical department, n (%)				0.703	
cardiac surgery	305	275 (28.74)	30 (23.62)		
Thoracic surgery	23	21 (2.19)	2 (1.57)		
Abdominal surgery	144	124 (12.96)	20 (15.75)		
Vascular surgery	31	27 (2.82)	4 (3.15)		
Orthopedic surgery	365	324 (33.86)	41 (32.28)		
others	216	186 (19.44)	30 (23.62)		
rCRI, n (%)				0.070	12
rCRI 1	440	387 (40.44)	53 (44.88)		
rCRI 2	268	230 (24.03)	38 (29.92)		
rCRI 3	236	209 (21.84)	27 (21.26)		
rCRI 4	128	121 (12.64)	7 (5.51)		
NYHA				0.231	14
NYHA I	445	388 (40.54)	57 (44.88)		
NYHA II	367	320 (33.44)	47 (37.01)		
NYHA III	236	217 (22.68)	19 (14.96)		
NYHA IV	22	20 (2.09)	2 (1.57)		
MoCA Sum(mean ± sd)	23.00 (± 3.94)	22.90 (± 3.94)	23.77(± 3.86)	0.017*	0
MoCA Education				< 0.001*	3
> 12 years	609	513 (53.61)	96 (75.59)		
≤ 12 years	473	443 (46.29)	30 (23.62)		
Laboratory values (median) [IQR]					
GLDH 37 C (U/l)	3.3 [2.25]	4.77 [5.1]	4.21 [3.2]	0.856	961
ALT(GPT) 37 C (U/l)	23 [16]	28 [20.64]	40.08 [56.77]	0.276	661
AST(GOT) 37 C (U/l)	25 [11]	31.19 [32.98]	28.02 [12.49]	0.675	669
gamma-GT 37 C (U/l)	34 [50]	75.16 [180.12]	133.93 [215.03]	< 0.001*	767
alk.Phosphatase 37 C (U/l)	79.5 [44.25]	113.87 [117.15]	141.23 [150.69]	0.477	992
Hemoglobine (g/dl)	13.4 [2.3]	13.17 [1.88]	13.53 [1.87]	0.036*	2
Creatinine (mg/dl)	0.9 [0.35]	1.06 [0.73]	1.01 [0.44]	0.781	2
CRP (mg/l)	3.26 [7.73]	12.15 [28.28]	9.36 [17.3]	0.828	9
Total proteine (g/l)	69.2 [6.9]	68.54 [6.02]	69.42 [5.58]	0.238	23

N = number, SSQ = single sentence question, *=significant with p-value < 0.05, sd = standard deviation, ASA = American Society of Anesthesiologist Score, rCRI = revised cardiac risk index, NYHA = New York Heart Association Score, MoCA (Montreal Cognitive Assessment), IQR = interquartile range, GLDH = Glutamate dehydrogenase, ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, GGT = gamma glutamyl transpeptidase, alk. Phosphatase = alkaline phosphatase, CRP = C-reactive protein

could lead to a better postoperative outcome by improving several organic dysfunctions and in consequence reducing postoperative morbidity [7]. Discontinuation of alcohol consumption four to eight weeks prior to any surgical procedure could potentially decrease the incidence of postoperative complications [24].

In the immediate clinical setting the early and accurate detection of patients with alcohol drinking problems can help to avoid the occurrence of an AWS (alcohol withdrawal syndrome) [5].

When choosing a screening tool for alcohol consumption in the daily clinical routine, it is important to

Table 2 Comparison of all patients that answered the AUDIT-C

	All AUDIT-C patients	AUDIT-C 0–3	AUDIT-C > 3	*p*-value	missings
Number	668	495	173		
Age(mean ± sd)	72.23 (± 7.39)	72.69 (7.37)	70.92 (7.34)	0.008*	0
Sex				< 0.001*	2
Female, n (%)	250 (37.54)	222 (44.85)	28 (16.18)		
Male, n (%)	416 (62.46)	271 (54.75)	145 (83.82)		
ASA, n (%)				0.372	9
1	17 (2.58)	12 (2.42)	5 (2.89)		
2	195 (29.59)	139 (28.08)	56 (32.37)		
3	395 (59.94)	295 (59.60)	100 (57.80)		
4	51 (7.74)	43 (8.69)	8 (4.62)		
5	1 (0.15)	1 (0.20)	0 (0.00)		
Surgical department, n (%)				0.286	0
cardiac surgery	228 (34.13)	177 (35.76)	51 (29.48)		
Thoracic surgery	17 (2.54)	13 (2.63)	4 (2.31)		
Abdominal surgery	78 (11.68)	58 (11.72)	20 (11.56)		
Vascular surgery	18 (2.69)	13 (2.63)	5 (2.89)		
Orthopedic surgery	201 (30.09)	151 (30.51)	50 (28.90)		
others	126 (18.86)	83 (16.77)	43 (24.86)		
rCRI, n (%)				0.057	11
rCRI 1	256 (38.96)	190 (38.38)	66 (38.15)		
rCRI 2	161 (24.51)	113 (22.83)	48 (27.75)		
rCRI 3	157 (23.90)	114 (23.03)	43 (24.86)		
rCRI 4	83 (12.63)	71 (14.34)	12 (6.94)		
NYHA, n (%)				0.668	13
NYHA I	259 (39.54)	187 (37.78)	72 (41.62)		
NYHA II	234 (35.73)	173 (34.95)	61 (35.26)		
NYHA III	150 (22.90)	116 (23.43)	34 (19.65)		
NYHA IV	12 (1.83)	10 (2.02)	2 (1.16)		
MoCA Sum(mean ± sd)	23.43 (± 3.86)	23.2 (± 3.9)	24.09 (± 3.69)	0.011*	
MoCA Education				0.003*	
> 12 years	389 (58.41)	269 (54.34)	120 (69.36)		
≤ 12 years	279 (41.89)	226 (45.66)	53 (30.64)		
Laboratory values (median) [IQR]					
GLDH 37 C (U/l)	3.3 [2.4]	3.4 [2.37]	2.9 [2.4]	0.363	567
ALT(GPT) 37 C (U/l)	23 [16.75]	23 [16]	25 [16]	0.233	378
AST(GOT) 37 C (U/l)	26 [11]	25.5 [11]	26 [11]	0.579	379
gamma-GT 37 C (U/l)	35.5 [52.5]	32 [37.75]	49 [83.75]	0.014*	462
alk.Phosphatase 37 C (U/l)	75 [47]	74 [46.5]	85.5 [46.25]	0.507	615
Hemoglobine (g/dl)	13.5 [2.3]	13.35 [2.2]	13.95 [2.5]	0.003*	2
Creatinine (mg/dl)	0.9 [0.34]	0.9 [0.35]	0.9 [0.32]	0.667	2
CRP (mg/l)	3.2 [7.77]	3.24 [8.3]	3.08 [6.74]	0.930	8
Total proteine (g/l)	69 [7.25]	69 [7.4]	68.8 [7.2]	0.893	17

N = number, SSQ = single sentence question, *=significant with p-value < 0.05, sd = standard deviation, ASA = American Society of Anesthesiologist Score, rCRI = revised cardiac risk index, NYHA = New York Heart Association Score, MoCA (Montreal Cognitive Assessment), IQR = interquartile range, GLDH = Glutamate dehydrogenase, ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, GGT = gamma glutamyl transpeptidase, alk. Phosphatase = alkaline phosphatase, CRP = C-reactive protein

consider the time that both, physician and patient, are willing and able to provide for this procedure. Time-consuming assessments can strain both the respondent's willingness and capacity to provide complete and accurate responses [25]. Surgeons indicated, that they preferred the use of a clinical assessment to a screening questionnaire, due to lack of time, busy schedules, and lengthy consent forms for surgery [26, 27]. Additionally, anesthetists tend to hand out the screening questionnaire selectively to intoxicated patients or known chronic high level drinking patients [26].

Additionally, detection of risky alcohol intake needs to be accurate taking into consideration that reliable testimony about alcohol consumption could depend on

Table 3 Distribution of AUDIT-C results in patients that answered the SSQ in the negative

	All Patients (% of all patients with neg. SSQ and pos. AUDIT-C)	Women (% of women with neg. SSQ and pos. AUDIT-C)	Men (% of men with neg. SSQ and pos. AUDIT-C)	misss-ing
Negative SSQ and positive AUDIT-C (≥ 1)	375	115 (30.75)	259 (68.98)	1
Low or infrequent consumption (%)	281 (74.87)	101 (87.80)	178 (68.73)	2
AUDIT-C = 1 (%)	93 (24.87)	46 (40.00)	47 (18.15)	0
AUDIT-C = 2 (%)	93 (24.60)	31 (26.96)	61 (23.55)	1
AUDIT-C = 3 (%)	95 (25.40)	24 (20.87)	71 (27.41)	0
Significant consumption (%)	94 (25.13)	14 (12.18)	80 (30.89)	
Moderate alcohol consumption (%)				
AUDIT-C = 4 (%)	42 (11.23)	9 (2.41)	33 (12.74)	0
Frequent and/or high consumption (%)	52 (13.90)	5 (1.34)	47 (18.15)	
AUDIT-C = 5 (%)	26 (6.95)	5 (1.34)	21 (8.11)	0
AUDIT-C = 6 (%)	10 (2.67)	0	10 (3.86)	0
AUDIT-C = 7 (%)	11 (2.94)	0	11 (4.25)	0
AUDIT-C = 8 (%)	3 (0.80)	0	3 (1.16)	0
AUDIT-C = 9 (%)	2 (0.53)	0	2 (0.77)	0

AUDIT-C = Alcohol Use Disorder Identification Test- Consumption, SSQ = Single Sentence Question

the setting in which the interview is posed. A person to person interview regarding a sensitive topic like alcohol consumption can lead to evasive answers. Kip et al. found that the prevalence rate of AUD determined by anesthesiologists was 6.9% compared to 18.1% if AUD was assessed using a computerized version of the AUDIT [28]. Inaccurate assessment of alcohol consumption may lead to the selective identification of individuals with severe alcohol dependency while overlooking patients who drink above recommended limits [26].

The results of our study show, that patient´s responses can differ considerably depending on how alcohol use is addressed during the routine pre-clinic visit prior to hospital admission. Of the patients that negated the SSQ about daily alcohol consumption and scored positive on the AUDIT-C questionnaire, 25.1% reported moderate (11.2%) to high (13.9%) alcohol consumption.

Significantly more men than women confirmed daily alcohol consumption ($p < 0.001$). This is in accordance with other surveys and studies about alcohol consumption [1, 21, 29–32]. The lower rate in our study sample could be influenced by the fact that it comprised of older patients.

Education level was significantly higher in patients that confirmed daily alcohol consumption ($p = 0.0017$) and scored moderate to high on the AUDIT-C ($p = 0.003$). A Danish study in middle-aged men and women found no significant differences of the alcohol consumption groups in age, but a significantly lower education in abstinent study participants [32]. The higher educational level of patients confirming daily alcohol intake ($p < 0.001$) and patients with an AUDIT-score > 3 ($p = 0.003$) could be an explanation for the fact that those patients also scored significantly higher in the MoCA test ($p = 0.017$ and $p = 0.011$, respectively).

The AUDIT-C has proven its sensitivity and specificity in various different settings and appears to be as good as if not better than the AUDIT [33] and national guidelines recommend the AUDIT questionnaire as a screening tool of at-risk alcohol consumption, harmful use or alcohol dependence and suggest the use of the AUDIT-C if the AUDIT is too complex or time is limited [34, 35].

An entity that has to be considered in the decision for a screening tool to accurately detect alcohol consumption in older patients is the possible presence of MCI (Mild Cognitive Impairment). According to Nasraddine et al. a result < 26 in the MoCA test could indicate a mild cognitive impairment [36]. The mean sum in the MoCA test was 23.00 in our study group with a mean age just above 72 years. This indicates that the presence of MCI has to be seriously considered in this patient group. Self-reports of older respondents (+ 70 years of age) with reduced working memory capacity are particularly affected by increased question difficulty [37]. Therefore, short questions and helpful explanations in a setting that provides enough time for the answers might help to evaluate information about alcohol consumption correctly. Paper-based or electronic versions of the AUDIT-C could be handed out to the patients before their face-to-face visit with the anesthesiologist in order to give the patient enough time to answer the questions.

The AUDIT-C could be completed by most patients without additional guidance, enables the treating physician to add important information to the patient's preoperative condition, and could be easily provided and completed paper-based or electronically. The use of electronic devices such as a computer or tablet has many advantages. It is cost-effective as it saves valuable face-to-face time with the anesthesiologist for personal questions regarding the upcoming surgery. Questionnaires could be

Table 4 Comparison of all patients that confirmed daily alcohol consumption in regards to their alcohol consumption according to the AUDIT-C

	All AUDIT-C patients	AUDIT-C 0–3 SSQ pos	AUDIT-C > 3 SSQ pos	missings
Number				
Age(mean ± sd)	71.24 (± 7.6)	68 (± 10.8)	71.41 (± 7.46)	0
Sex	83	4	79	0
Female, n (%)	16	2	14	
Male, n (%)	67	2	65	
ASA, n (%)				2
1	3	0	3	
2	27	1	26	
3	50	3	47	
4	1	0	1	
5	0	0	0	
Surgical department, n (%)				0
cardiac surgery	22	2	20	
Thoracic surgery- lung etc., esophagus	1	0	1	
Abdominal surgery	13	1	12	
Vascular surgery	3	0	3	
Orthopedic surgery	24	0	24	
others	20	1	19	
rCRI, n (%)				2
rCRI 1	35	2	33	
rCRI 2	23	0	23	
rCRI 3	18	1	17	
rCRI 4	5	1	4	
NYHA, n (%)				2
NYHA I	34	3	31	
NYHA II	32	0	32	
NYHA III	14	1	13	
NYHA IV	1	0	1	
MoCA Sum(mean ± sd)	23.95 (± 3.95)	22.5 (± 5.74)	24.03 (± 3.87)	0
Min - max values	14–30	15–27	14–30	
MoCA Education				
> 12 years	60	2	58	
≤ 12 years	23	2	21	
Laboratory values (median) [IQR]				
GLDH 37 C (U/l)	2.9 [2.93]		2.9 [2.93]	71
ALT(GPT) 37 C (U/l)	23.5 [16.75]	36.5 [18.5]	23.5 [16.25]	45
AST(GOT) 37 C (U/l)	24.5 (10.75]	49 [17]	23.5 [8.5]	47
gamma-GT 37 C (U/l)	59.5 [100.25]	91 [0]	57 [104.5]	55
alk.Phosphatase 37 C (U/l)	118.5 [74.5]	120 [0]	117 [93]	75
Hemoglobine (g/dl)	13.75 [2.68]	12.35 [0.7]	13.85 [2.65]	1
Creatinine (mg/dl)	0.87 [0.24]	1.18 [0.18]	0.86 [0.25]	1
CRP (mg/l)	3.03 [6.73]	4.09 [4.82]	3.02 [6.73]	2
Total proteine (g/l)	68.8 [6.6]	69.95 [2.72]	68.8 [7.6]	2

N = number, SSQ = single sentence question, *=significant with p-value < 0.05, sd = standard deviation, ASA = American Society of Anesthesiologist Score, rCRI = revised cardiac risk index, NYHA = New York Heart Association Score, MoCA (Montreal Cognitive Assessment), IQR = interquartile range, GLDH = Glutamate dehydrogenase, ALT = Alanine aminotransferase, AST = Aspartate aminotransferase, GGT = gamma glutamyl transpeptidase, alk. Phosphatase = alkaline phosphatase, CRP = C-reactive protein

programmed to allow only valid and consistent responses [25]. If necessary pictures of beverage containers or explanations could be included that facilitate the understanding of standard drink sizes further [38]. Patients that are unable or unwilling to use an electronic device can fill in a paper-based version of the AUDIT-C during their pre-clinic assessment visit, maybe assisted by an interviewer that can provide motivation and clarification,

but their presence may negatively affect the respondent´s willingness to answer sensitive questions [25].

To support the results of alcohol consumption questionnaires further blood biomarkers could be taken into consideration. Assessment of current levels of intoxication might include the direct biomarkers Blood Alcohol concentration (BAC), phosphatidyl ethanol (Peth), and fatty acid ethyl ester (FAEE) [39]. The indirect alcohol biomarkers, such as MCV (mean corpuscular volume), AST (aspartate aminotransferase), ALT (alanine aminotransferase), GGT (gamma glutamyl transpeptidase), and CETP (cholesteryl ester transfer protein), could indicate heavy alcohol use indirectly, as they are mainly correlated to the impact of chronic alcohol use on the liver and red blood cells [39]. One has to bear in mind that they are greatly influenced by factors, such as age, sex, and/or organ damage [40]. As the laboratory values of the PROPDESC study were collected to screen for possible POD-predicting indicators the availability of the indirect alcohol biomarkers for additional evaluation were very limited. Still we found a difference in GGT value in the SSQ sample as well as the AUDIT-C sample with patients reporting higher amounts of alcohol consumption having significantly higher values of GGT ($p < 0.001$). Even though GGT is widely used as a biomarker for sustained excessive alcohol intake [39], its specifity is reduced with comorbid medical conditions not related to alcohol (e.g. nonalcoholic liver diseases, nephrotic syndrome, and pancreatitis [41]). Even though high MCV may indicate excessive drinking, we did not include it in our analysis as it is neither sensitive nor specific for alcohol use and factors such as age, sex, and pre-existing conditions can influence the results [39]. Furthermore, the following limitations associated with the use of blood biomarkers for alcohol use have to be considered: firstly, currently used biomarkers could differentiate between excessive alcohol use and abstinence, but lack precise quantitative information about the amount of consumption [39]. Blood biomarkers could not detect detailed drinking patterns and their sensitivity and specificity is influenced by comorbid health problems [39].

Limitations: The study excluded younger patients and patients with difficulties in the German language or those with pre-existing cognitive impairments like dementia. While this is understandable for the accuracy of the study, it limits the inclusivity of the sample and may not fully reflect the alcohol consumption patterns in these excluded populations. The PROPDESC study was conducted in a mono-centric setting. This limits the generalizability of the results to other populations or regions, as different hospitals may have different patient demographics, healthcare practices, and cultural contexts regarding alcohol use.

Both assessments were done by study personnel composed of Study Nurses and medicinal students in the context of the PROPDESC study. In such a scenario, there could be a response bias since the desire to portray a favorable image significantly influences self-reported alcohol consumption [42]. Furthermore, the study assessment was conducted apart from the anesthesiological evaluation. Patients might be more honest about their drinking habits when asked by their surgeon or anesthesiologist, because they might be more aware of the relevance of a correct answer.

Conclusions

The method of questioning influences the accuracy of the information older patients provide about their alcohol consumption during pre-clinic visits. A single sentence question about daily alcohol consumption could fail to identify patients with possibly health- and surgery-relevant alcohol consumption levels and anesthesiologist might miss the opportunity to implement necessary prevention measures to avoid AWS in patients with severe AUD. The AUDIT-C could evaluate the patient´s alcohol intake more precisely than a single sentence question without the need of considerably more time as it could be easily self-administered. It should therefore be added to the routine assessment at the pre-hospital visit of the patient. The AUDIT-C is a suitable tool to assess a patient´s alcohol consumption level. Additionally, answering a questionnaire provides initiative to the patient and a more objective assessment to the physician. Furthermore, it could relieve both from sensing a moral evaluation of the patient´s alcohol consumption level.

Abbreviations

WHO	World Health Organisation
PROPDESC-study	Pre-Operative Prediction of postoperative delirium by appropriate Screening-study
APC	Per capita alcohol consumption
EU	European Union
AUDIT-C	Alkohol Use Disorder Identification Test-Consumption
AUDIT	Alkohol Use Disorder Identification Test
AWS	Alcohol Withdrawal Syndrome
ASPSTF	The U.S. Preventive Service Task Force
NIAAA	National Institute on Alcohol Abuse and Alcoholism
SASQ	Single Alcohol Screening Question
SSQ	Single sentence question
POD	Postoperative delirium
ASA	American Society of Anesthesiologists class
NYHA	New York Heart Association
rCRI	Revised cardiac risk index
MoCA	Montreal Cognitive assessment
AUD	Alcohol Use disorder
GGT	Gamma Glutamyl Transpeptidase
MCI	Mild Cognitive Impairment

Supplementary Information

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Supplementary Material 1

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Author contributions
All authors contributed to the study conception and design. Conceptualization was done by JM and VG. Methodology and funding acquisition were performed by JM and MW, Supervision was provided by MW. The first draft of the manuscript was written by VG. All authors revised the manuscript critically and read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Ethics vote for the PROPDESC study was obtained from the Ethics Committee of the Medicinal Faculty of the Rheinische Friedrich-Wilhelms-Universität Bonn in 2017 (lfd. Nr. 255/17). All procedures were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000 (5). Informed consent was obtained from all individual participants included in the study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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ORIGINAL RESEARCH

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Predictiveness of preoperative laboratory values for postoperative delirium

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Abstract

Background: Postoperative delirium (POD) is a common postoperative complication, especially in patients over 60 years, with an incidence ranging from 15% to 50%. In most cases, POD manifests in the first 5 days after surgery. Multiple contributing risk factors for POD have been detected. Besides the predisposing factors such as higher age, cognitive impairment, high blood pressure, atrial fibrillation, and past stroke, pathophysiological mechanisms like neuroinflammation are also considered as contributing factors.

Methods: In a subanalysis of the "PRe-Operative Prediction of postoperative DElirium by appropriate SCreening" (PROPDESC) study, the preoperative laboratory values of sodium, potassium, total protein, hemoglobin concentration (Hgb), and white blood cells as well as the biomarkers creatinine, HbA1c, NT-pro-BNP, high sensitive Troponin T (hsTnT), and C-reactive protein (CRP) were assessed to investigate a possible relationship to the occurrence of POD.

Results: After correction for age, physical status classification, surgery risk after Johns Hopkins, and operative discipline (cardiac surgery vs. noncardiac surgery), male patients with a Hgb <13 g/dL had significantly higher odds for POD ($p = 0.025$). Furthermore, patients with CRP ≥ 10 mg/L, HbA1c value ≥ 8.5% as well as patients with hypernatraemia (>145 mmol/L) presented significantly higher odds to develop POD ($p = 0.011$, $p < 0.001$, and $p = 0.021$, respectively). A raised (>14–52 ng/L) or high (>52 ng/L) hsTnT value was also associated with a significantly higher chance for POD compared to the patient group with hsTnT <14 ng/L ($p < 0.001$ and $p = 0.016$, respectively).

Conclusions: Preoperative Hgb, CRP, HbA1c, sodium, and hsTnT could be used to complement and refine the preoperative screening for patients at risk for POD. Further studies should track these correlations to investigate the potential of targeted POD protection and enabling hospital staff to initiate POD-preventing measures in time.

Vera Guttenthaler and Jacqueline Fidorra contributed equally to this work.

Results of this manuscript were presented on the HAI (Capitol-congress of the German Society of Anaesthesiology and Intensive Care) in Berlin in 2022.

KEYWORDS

older adults, postoperative delirium, routine laboratory parameters

1 | INTRODUCTION

Postoperative delirium (POD) is, especially for patients older than 60 years, a common postoperative complication with an incidence between 15% and 50%.[1–3] According to the International Statistical Classification of Diseases and Related Health Problems, 11th revision (ICD-11), "delirium is characterized by a disturbance of attention, orientation, and awareness that develops within a short period of time, typically presenting a significant confusion or global neurocognitive impairment and may be caused among others by multiple or unknown etiological factors."[4]

In addition, it represents a major economic burden for the healthcare systems.[5,6]

Identifying high-risk patients and taking appropriate measures to prevent delirium in these patients is of particular importance, as treatment options have shown only insufficient effect.[7]

A possible pathophysiological mechanism, that might contribute to the occurrence of delirium is neuroinflammation.[5] Liu et al. found that POD is accompanied by postoperatively raised values of C-reactive protein (CRP) and interleukin-6.[8] Among others, neuroinflammation induces changes of the synaptic plasticity, which might explain cognitive dysfunction during episodes of POD.[9]

HbA1c (glycated hemoglobin value) could mirror reoccurring or persisting hyper-glycaemia; both are known for enhancing inflammation and oxidative stress.[10,11] It is anticipated that cerebral-ischemic events could also contribute to the incidence of POD. Additionally, preoperative anemia could lead to a cognitive dysfunction postoperatively.[12]

A possible influence of hypo- and hypernatremia on the development of POD has still to be clarified, as some studies found a positive correlation of sodium levels with POD[13,14] whereas others found no relationship.[15,16] Additionally, a review published in 2023 by Hoogma et al. identified—among many other factors—anemia, infections malnutrition, metabolic derangements, and dehydration as predisposing and precipitating risk factors for POD.[17] Another review by Mevorach et al. found low hematocrit; low hemoglobin, low serum albumin and potassium levels; increased values of creatinine, CRP, and white blood cell count; and low as well as increased serum sodium again among other variables to be potentially representative of a POD risk profile.[18]

In the context of myocardial oxygen debt troponin release is indicating coronary insufficiency. N-terminal pro b-type natriuretic peptide (NT-pro-BNP) is released by stretching myocytes and thus reflecting heart failure.

The correlation of these cardiac biomarkers with increased POD risk might be explained by their association triggers of delirium such as impaired cerebral perfusion,[19,20] systemic inflammation,[21] or cardio-embolic events.[22]

Therefore, it is of interest whether routinely taken preoperative blood parameters could reveal a predisposition for POD and indicate preventive measures in patients at risk. The aim of this analysis was to examine which preoperative routine blood parameters could be used to estimate the patients' risk for POD.

Key points

- Postoperative delirium (POD) is the most common postoperative complication that older people suffer after surgery and is associated with severe consequences like prolonged hospital stay, increased cognitive and noncognitive morbidity, reduced quality of life, and raised 180 days mortality.
- We confirmed known risk factors for POD like older age, male sex, American Society of Anaesthesiologist score ≥III, higher surgical risk, and especially cardiac surgery in our study.
- Concentrations of HbA1c ≥ 8.5%, C-reactive protein ≥ 10 mg/L, hypernatremia >145 mmol/L, Troponin-T >14 ng/L, and preoperative anemia in men (Hb <13 g/dL) were identified as significant risk factors for POD.

2 | METHODS

2.1 | Study design

The evaluation is based on the results of the monocentric observational study "PRe-Operative Prediction of postoperative DElirium by appropriate SCreening" (PROPDESC). PROPDESC was conducted in 2018 and 2019 at the University Hospital in Bonn to develop a quickly applicable risk score to identify patients at risk for POD in preoperative routine.[23,24] Ethics vote was provided by the Ethics Commission of the Medicinal Faculty of the Rheinische Friedrich-Wilhelms Universität Bonn in 2017 (Application Nr. 255/17). Patients were screened for eligibility during their preoperative evaluation by the department of anaesthesiology. Blood samples were taken for preoperative cardiac risk screening before elective surgery. To classify their preoperative condition the following parameters were assessed: age, gender, ASA (American Society of Anaesthesiologist) physical status classification, surgical risk after Johns Hopkins (modified three-step scale after Donati 2004),[25] surgical discipline, and preoperative lab values for cardiac risk screening.

After elective surgery POD was assessed on the first five postoperative days via CAM-ICU (Confusion Assessment Method for Intensive Care Units) on the intensive care ward if the patients' Richmond agitation and sedation scale score was ≥ −3 and by CAM and 4-AT (4-A Test—Alertness, Abbreviated mental test, Attention test and Acute change of fluctuating course) if the patient was located on the normal ward.

Additionally, the Delirium observation scale was used on normal wards and ICU to improve the sensitivity of POD assessment. Patients were tested once a day, in the morning, by trained study personnel composed of physicians and medical students. Assessment was scheduled to be finished before lunchtime and was valid if the testing was conducted on 3 consecutive days.

POD was considered present, if one of the applied tests was positive on one test-occasion. Patients were considered non-delirious if they were not tested positive for POD or left hospital before the end of testing period. Additionally, preoperative assessments for mild cognitive impairment, alcohol consumption, and quality of life was done. Study personnel conducted a follow-up to assess quality of life 180 days after surgery.[23]

2.2 | Participants

Inclusion criteria were a minimum age of 60 years, elective surgery scheduled for at least 60 min in various surgical departments of the university hospital except neurosurgery and written informed consent to study participation. Exclusion criteria were emergency procedures as well as apparent problems with the German language, illnesses who could compromise patients' safety or the correct assessment of POD and presumed insufficient compliance to the study procedures.

2.3 | Variables

All investigated laboratory values are part of preoperative cardiac risk screening and act as surrogate parameters for organ functions. The screening includes hemoglobin concentration, HbA1C, CRP, leukocyte count, creatinine concentration, the amount of serum total protein, the concentrations of sodium and potassium as well as the cardiac biomarkers high-sensitive Troponin-T (hsTnT), and NT-pro-BNP.

The HbA1c value was chosen as a reference value for poorly adjusted diabetes, creatinine as an indicator for a possible reduction in renal function, CRP and leukocytes for the detection of inflammatory disposition, Sodium and potassium as indicators for disturbed electrolyte balance, hsTnT for myocardial injury, NT-pro BNP for indicating cardiac performance respectively cardiac stress, and hemoglobin concentration to detect preoperative anemia. POD correlation with preoperative hemoglobin concentration was analyzed in different ways: considering gender-specific cut-off values for anemia and using a gender-neutral cut-off value.

We assessed all laboratory values via the patients' in-hospital file.

2.4 | Statistical methods

For statistical analysis, we categorized the laboratory values and biomarker values using different approaches. The categorization of potassium (K), sodium (Na), total protein, leukocytes, and HbA1c was as follows: group 1 (reference group): values within the reference ranges of the central laboratory of the University Hospital Bonn (K = 3.5–5.1 mmol/L; Na = 136–145 mmL/L; total protein = 64–83 g/L, leukocytes = 3.6–10.5 G/L, HbA1c = 6.45–8.49%). According to the German Diabetes Society (DDG), a HbA1c value ≥ 8.5% is considered strongly elevated.[26]

Group 2 includes values below, and group 3 values above the reference ranges of the respective parameters.

Creatinine values were divided into two groups: Group 1 (reference group): values within the reference range of the central laboratory of the University Hospital Bonn (0.5–0.9 mg/dL), group 2: values above the reference.

Using CRP as an indicator for POD, we chose a cut-off value of 10 mg/L as our collective consisted only of elective patients.

HsTnT was categorized into three groups: (1) values ≤ 14 ng/L (within the reference range), (2) values between >14 and 52 ng/L, and (3) values above 52 ng/L (roll-in cut-off for the diagnosis of NSTEMI).

NT-pro-BNP values above 30 mg/dL are associated which more cardiovascular events preoperatively, according to the Canadian Cardiovascular Society. Therefore, the collective was categorized into (1) below and (2) above 30 mg/dL.

Correlation of preoperative anemia and POD was also analyzed in different approaches. Gender-indifferent consideration was done following the Guidelines of the German Medical Association, using a cut-off value of ≥10 g/dL[27] and gender-segregated categorization divided patients into two groups using the World Health Organization reference values for anemia, that are <12 g/dL for nonpregnant women and <13 g/dL for men.[28]

We considered differences statistically significant at a significance level of 5% ($\alpha = 0.05$) with a probability of 80% ($\beta = 0.20$).

We checked data for completeness and normal distribution of values and used the χ^2 test to compare patient groups with and without POD on binary categorical variables. The Mann–Whitney U test was used for metric or ordinal scaled variables,[29] and we tested all variables for multicollinearity.

The following characteristics were established as reference for the OR: age 60–69 years, female gender, ASA score I, Johns Hopkins low surgical risk, and noncardiac surgery.

An adjusted multivariable binary logistic regression was performed to determine the influence of the considered laboratory parameters. We used the set categories to classify the values in the clinical context on the basis of reference ranges or cut-offs defined above. As influencing cofactors age, ASA physical status classification,[30–32] surgical risk according to Johns Hopkins,[25,33] and discrimination between cardiac surgery and noncardiac surgery (HCH/NHCH) were considered since they may influence the biomarkers as well as the primary endpoint (POD). These cofactors have been shown to be significant risk factors for POD in previous studies.[15,34–36] IBM SPSS Statistics 25 was used for all analyses.

3 | RESULTS

We recruited 1097 patients for the PROPDESC study. There were 76 dropouts, of which 72 patients did not undergo surgery and four patients subsequently withdrew their consent to the study. Fifteen

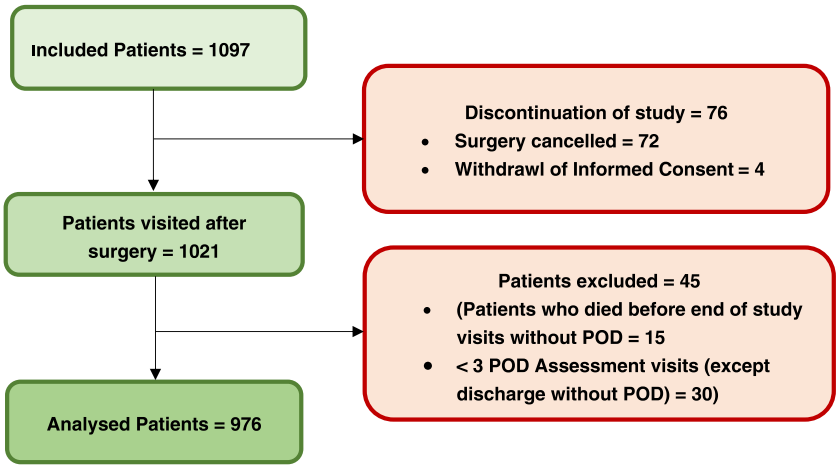

FIGURE 1 Patients participating in the PROPDESC study (modified after Menzenbach et al. 2022).[24] POD, postoperative delirium.

patients died without manifesting POD. Thirty patients had fewer than three completed visits without developing POD. In total, 976 patients were included in the analysis (Figure 1).

3.1 | Descriptive results

The mean age in the total collective was 72.3 ± 7.3 years. Gender distribution was 38.4% women and 61.6% men. Of 976 patients, 229 (23.5%) developed POD. Divided into age groups—19.8% of those aged 60–69 years, 24.7% of those aged 70–79 years (OR 1.3), 28.8% of those aged 80–89 years, and 28.6% of patients aged 90 years and older developed POD (OR 1.6 for both groups).

3.2 | POD-risk

With rising age, the incidence of POD increased significantly ($p = 0.016$). The chance of developing POD was significantly higher for men compared to women ($p < 0.001$; OR = 1.8) (Table 1).

ASA score, surgical risk, and type of surgery were significantly related to the occurrence of POD, with $p < 0.001$ each (Table 1). The risk of developing POD was significantly higher for patients undergoing cardiac surgery compared to noncardiac surgery patients ($p < 0.001$; OR 6.8) (Table 1).

3.3 | Blood parameters

32.2% of patients with a preoperative hemoglobin value < 10 g/dL were postoperatively delirious compared to 22.9% of patients with hemoglobin ≥10 g/dL (OR 1.9). 22.4% of women with preoperative anemia (<12 g/dL) developed POD. Women without preoperative anemia developed POD in 15.2% (p: 0.131). Preoperative anemia (<13 g/dL) increased the risk of developing POD in men (p: 0.025; OR 1.7) (Table 2).

In patients with elevated HbA1c (6.41%–8.49%), 30.9% and in patients with severely elevated HbA1c (≥8.5%), 64% developed POD. Patients with preoperatively severely elevated HbA1c (≥8.5%) developed POD significantly more often ($p < 0.001$; OR 6.0) (Table 2) than patients without an elevated HbA1c.

Patients with a preoperative CRP above the cut-off value of 10 mg/L had a significantly higher POD occurrence than patients with a preoperative CRP below 10 mg/L ($p = 0.011$; OR 1.7) (Table 2).

The POD rate of patients with normal concentration of leukocytes (3.6–10.5 G/L), of patients with leukocytosis (>10.5 G/L), and of patients with leukocytopenia (<3.6 G/L) differed not significantly (Table 3).

The preoperative creatinine value had no significant impact on POD occurrence (Table 3).

High total protein (>83 g/l) was found in three patients who did not develop POD. The correlation between the preoperative protein values and the occurrence of POD was not significant ($p = 0.053$) (Table 3).

22.7% of patients with preoperative normal sodium (136–145 mmol/L) and 43.8% of patients with preoperative hypernatremia (>145 mmol/L) developed POD. Of patients with preoperative hyponatremia (<136 mmol/L), 28.6% were found to be delirious after surgery. Patients with elevated sodium levels had higher odds to develop POD (p: 0.021; OR 3.8). Compared to patients with normal preoperative sodium values POD incidence of patients with hyponatremia was not significantly higher (Table 3).

23.5% of patients with preoperative normal potassium (3.5–5.1 mmol/L), 18.5% of patients showing preoperative hyperkalemia (>5.1 mmol/L), and 40.0% of patients with hypokalemia (<3.5 mmol/L) developed POD. These differences were not statistically significant (hyperkalemia $p = 0.963$; hypokalemia $p = 0.066$) (Table 3).

16.7% of patients with normal Troponin T (≤14 ng/L), 32.3% of patients with slightly elevated Troponin T (14.01–52 ng/L), and 46.0% of patients with clearly elevated Troponin T (>52 ng/L) were diagnosed with POD. The incidence of POD was significantly higher

TABLE 1 POD in relation to demographic and surgical factors.

	Total	POD (%)	No POD (%)	OR	*p* Value	Missing
Age (years) total (mean ± SD)	72.3 ± 7.3	73.3 ± 7.2	72.0 ± 7.3		0.016*	0
60–69	388	77 (19.8%)	311 (80.2%)			
70–79	421	104 (24.7%)	317 (75.3%)	1.3		
80–89	160	46 (28.8%)	114 (71.2%)	1.6		
>90	7	2 (28.6%)	5 (71.4%)	1.6		
Sex					<0.001*	0
Female	375	64 (17.1%)	311 (82.9%)			
Male	601	165 (27.5%)	436 (72.5%)	1.8		
ASA					<0.001*	0
I	25	4 (16.0%)	21 (84.0%)			
II	339	31 (9.1%)	308 (90.8%)	0.5		
III	544	164 (30.1%)	380 (69.9%)	2.3		
IV	68	30 (44.1%)	38 (55.9%)	4.1		
Surgical risk					<0.001*	0
Low	126	3 (2.4%)	123 (97.6%)			
Moderate	430	70 (16.3%)	360 (83.7%)	8.0		
High	420	156 (37.1%)	264 (62.9%)	24.2		
Surgical discipline					<0.001*	0
Noncardiac surgery	702	91 (13.0%)	611 (87.0%)			
Cardiac surgery	274	138 (50.4%)	136 (49.6%)	6.8		

Abbreviations: ASA, American Society of Anaesthesiologists classification; OR, odds ratio; POD, postoperative delirium; SD, standard deviation.

*Clinically significant with $p < 0.05$, χ^2 test was used for the variables sex and surgical discipline, Mann–Whitney *U* test for the variables age, ASA class, and surgical risk.

in patients with a slight ($p < 0.001$; OR 2.1) and clearly elevated Troponin T ($p = 0.016$; OR 2.7) (Table 2).

17.5% of patients with preoperative NT-pro-BNP < 30 mg/dL developed POD, while 30.4% of patients with NT-pro-BNP ≥ 30 mg/dL showed POD. This difference was statistically not significant ($p = 0.300$) (Table 3).

4 | DISCUSSION

In the collective of the PROPDESC study, 23.5% of the patients developed delirium after their surgery. Patients' age was found to be an independent risk factor for POD in this sample. These findings are consistent with the literature.[1,18,35,37] More men than women developed POD in our study, which also supports the tendencies in other studies. Furthermore, ASA score ≥III[30] and level of surgical risk according to Johns Hopkins[25] were seen as significant risk factors for POD. ASA status >2 was found to be a risk factor in the review done by Mevorach,[18] while a high-risk surgical procedure was mentioned as a precipitation factor for POD in another review by Hoogma[17] Cardiac surgery was associated with a substantially higher risk of POD than other surgical disciplines and thus may be considered a risk factor itself.

Several preoperative laboratory parameters interpreted as surrogate markers of organ function and metabolic status were associated with POD risk.

Regarding electrolytes, hypernatremia was found to be significantly associated with POD, although it occurred only in few patients ($n = 16$) within the investigated cohort. This result is consistent with the findings in the review by Mevorach et al.[18] In contrast, significantly more patients with preoperative hyponatremia <130.0 mmol/L or hypokalemia <3.0 mmol/L developed POD in the study sample of Kim et al.[15] Preoperative hyponatremia, hypokalemia or hyperkalemia were no significant risk factor in our patient population, but we had only two patients with hypokalemia <3.0 mmol/L and eight patients with hyponatremia <130.0 mmol/L, from which no valid conclusions could be drawn. It should be noted that the study by Kim et al. also included emergency patients who might show more often abnormal electrolyte concentrations than elective patients. Radke et al. discovered prolonged fasting time without fluid intake >6 h as an independent risk factor for the development of POD,[38] whereas Scholz et al. and Smulter et al. did

TABLE 2 Significant preoperative routine marker.

	Total number of patients	POD (%)	No POD (%)	OR	CI (95%)	*p* Value
Hb (g/dL)						0.050
≥10	917	210 (22.9%)	707 (77.1%)			
<10	59	19 (32.2%)	40 (67.8%)	1.9	1.0–3.5	
Hb (W) (g/dL)						0.131
≥12	277	42 (15.2%)	235 (84.8%)			
<12	98	22 (22.4%)	76 (77.6%)	1.7	0.9–3.2	
Hb (M) (g/dL)						
≥13	407	104 (25.6%)	303 (74.4%)			
<13	194	61 (31.4%)	133 (68.6%)	1.7	1.1–2.6	0.025*
Diabetes						
HbA1c (%)						
≤6.4	798	165 (20.7%)	633 (79.3%)			
6.4–8.49	139	43 (30.9%)	96 (69.1%)	1.4	0.9–2.2	0.117
>8.5	25	16 (64%)	9 (36%)	6.0	2.4–15.1	<0.001*
Inflammatory disposition						
CRP I (mg/L)						0.213
≤3	480	115 (24.0%)	365 (76.0%)			
>3	491	114 (23.2%)	377 (76.8%)	1.2	0.9–1.7	
CRP II (mg/L)						
<10	766	172 (22.5%)	594 (77.5%)			
≥10	210	57 (27.1%)	153 (72.9%)	1.7	1.1–2.5	0.011*
Electrolytes						
Sodium (mmol/L)						
136–145	897	204 (22.7%)	693 (77.3%)			
>145	16	7 (43.8%)	9 (56.2%)	3.8	1.2–11.7	0.021*
<136	63	18 (28.6%)	45 (71.4%)	1.5	0.8–2.7	0.247
Heart-related marker						
Troponin T (ng/L)						
≤14	586	98 (16.7%)	488 (83.3%)			
14.01–52	334	108 (32.3%)	226 (67.7%)	2.1	1.4–3.0	<0.001*
>52	50	23 (46.0%)	27 (54.0%)	2.3	1.2–4.5	0.016*

Abbreviations: CI, confidence interval; CRP, C-reactive protein; Hb, hemoglobin value; HbA1c, glycated hemoglobin value; M, men; OR, odds ratio; POD, postoperative delirium; W, women.

*Clinically significant with $p < 0.05$.

not see abnormal preoperative electrolyte levels as risk factors for POD.[15,16] Other studies found preoperative hypo- or hypernatremia as significant risk factors.[13,14,18]

The missing significance in the female group with preoperative anemia might be due to the lower number of female patients in the study (38.5%). Raats et al. found preoperative anemia (defined as Hb <7.6 mmol/L for women and <8.2 mmol/L for men) to be a significant risk factor for POD in both male and female patients[12] and two reviews list anemia as a predisposing factor.[17,39] Furthermore, Kim et al. saw preoperative hemoglobin <10 g/dL as a significant risk factor for POD. The German Medical Association recommends transfusions in patients with Hb <10 g/dL if there is evidence of anemic hypoxia.[27] However, intraoperative blood loss and transfusions are associated with the development of POD, likewise

TABLE 3 Nonsignificant preoperative routine marker.

	Total number of patients	POD (%)	No POD (%)	OR	CI (95%)	*p* Value
Inflammatory disposition						
Leukocytes (G/L)						
3.6–10.5	855	204 (23.9%)	651 (76.1%)			
>10.5	111	22 (19.8%)	89 (80.2%)	0.9	0.5–1.5	0.604
<3.6	10	3 (30.0%)	7 (70.0%)	1.9	0.4–8.6	0.411
Creatinine (mg/dL)						
≤1.2	807	177 (21.9%)	630 (78.1%)			
>1.2	169	52 (30.8%)	117 (69.2%)	1.2	0.8–1.8	0.441
Total protein (g/L)						
64–83	790	172 (21.8%)	618 (78.2%)			
>83	3	0	3 (100%)	0.0	0.0	0.999
<64	166	53 (31.9%)	113 (68.1%)	1.5	1.0–2.3	0.053
Electrolytes						
Potassium (mmol/L)						
3.5–5.1	890	209 (23.5%)	681 (76.5%)			
>5.1	65	12 (18.5%)	53 (81.5%)	1.0	0.5–2.0	0.963
<3.5	20	8 (40.0%)	12 (60.0%)	2.6	0.9–7.3	0.066
Heart-related marker						
NT pro-BNP (mg/L)						
<300	538	94 (17.5%)	444 (82.5%)			
≥300	378	115 (30.4%)	263 (69.6%)	1.2	0.8–1.8	0.300

Abbreviations: CI, confidence interval; M, men; NT-pro BNP, N-terminal pro b-type natriuretic peptide; OR, odds ratio; POD, postoperative delirium; W, women.

*Clinically significant with $p < 0.05$.

postoperative anemia.[12,15,40] Therefore, patient blood management is gaining importance as a preventive measure.

As patients in our investigated cohort with elevated (6.41% −8.49%) or severely elevated (≥8.5%) HbA1c were more likely to develop POD, a preoperative HbA1c level ≥8.5% could be considered as an independent risk factor for POD. Other studies have identified the preoperative presence of diabetes mellitus, elevated blood glucose levels, or high HbA1c as significant risk factors for the development of POD as well.[41–44] According to the DDG, patients undergoing elective surgery should aim at a preoperative HbA1c < 8.5%.[26] This recommendation is based on the thesis that patients with preoperatively elevated HbA1c develop significantly more often postoperative infections, acute kidney failure, and myocardial infarctions. They also tend to have a longer hospital stay and a lower 5-year survival rate.[45–48]

Furthermore, a preoperative CRP level ≥10 mg/L raised the risk of POD significantly. In the study by Kim et al., a preoperative elevated CRP level ≥10 mg/dL was considered a significant risk factor for POD. This was the only biomarker included in the DELPHI score by Kim to predict POD.[34] In a meta-analysis by Liu et al., 54 observational studies were evaluated considering the association of inflammatory markers and the occurrence of POD. In their overall view preoperative elevated CRP levels were considered as significant risk factors for POD, likewise postoperative elevated CRP and interleukin-6 levels.[14] Because inflammation and neuroinflammation are thought to be involved in the pathophysiology of delirium,[9,49,50] the role of preoperatively elevated CRP as a predisposing risk factor for POD is supported by these findings as well as through a large review on biomarkers of delirium in older people done by Toft at al. in 2019.[51]

According to several studies, cardiac surgery patients who developed POD had significantly higher preoperative creatinine values than patients who did not develop POD.[52–55] In contrast, a meta-analysis by Scholz et al. looking at visceral surgery patients showed that preoperative elevated creatinine levels do not have a significant impact on the development of POD.[15] Our results confirmed the finding by Scholz et al.

Several studies investigated the association between preoperative hypoalbuminaemia and the development of POD.[15,42,56] Low serum albumin concentrations can result from reduced protein

intake (e.g., malnutrition), protein loss (e.g., nephrotic syndrome), or reduced liver synthesis capacity (e.g., liver cirrhosis). Overall, albumin accounts for about 60% of total protein. In many studies, decreased preoperative albumin or total protein was shown to be a significant risk factor for POD.[15,34,42,56] In our patient sample, serum total protein was not associated with a significantly higher POD incidence.

In our mixed population of cardiac surgery and noncardiac surgery patients, a preoperatively mildly elevated (>14–52 ng/L) or markedly elevated troponin level (>52 ng/L) was found to be a significant risk factor for POD. However, patients with preoperative NT-pro-BNP value ≥ 300 mg/dL did not develop POD significantly more often.

Parente et al. showed that decompensated heart failure was a significant risk factor for the development of POD,[57] while Bucerius et al. also found a reduced ejection fraction ≤30% to be a risk factor for POD.[58] The association of cardiac biomarkers Troponin T and NT-pro-BNP with POD was also investigated. Tan et al. analyzing a small group of patients did not find elevated Troponin-T levels as significant risk factor for POD.[55] Uthamalingam et al. found a significant higher mean NT-pro-BNP value in patients who developed delirium.[59] It should be noted that the studies by Tan et al. and Uthamalingam et al. compared the mean values of preoperative Troponin T and NT-pro-BNP in patients with and without POD. Here outliers could have distorted these results. Additionally, the study by Uthamalingam et al. dealt with risk factors of general delirium and not only POD.

As a limitation of the statistical results, we have to point out that the biomarkers were evaluated in a univariate analysis. A multivariate analysis with all biomarkers was not performed, as only complete data sets could have been considered. Since there were some missing values for various biomarkers, this would have resulted in a considerable loss of data. To exclude a mutual influence of the biomarkers, the data were tested for multicollinearity, which was not found.

POD is the most common postoperative complication in the older population associated with severe consequences like prolonged hospital stay, increased cognitive and noncognitive morbidity, reduced quality of life, and raised 180 days mortality after surgery.[7,60]

Known risk factors for POD were confirmed to be older age, ASA score ≥III,[30] invasiveness of surgery in terms of higher surgical risk according to Johns Hopkins,[25,33] and especially cardiac surgery. In addition, significantly more men were affected by POD.

The preoperative biomarkers HbA1c ≥ 8.5%, CRP ≥ 10 mg/L, hypernatremia >145 mmol/L, and Troponin-T > 14 ng/L were identified as significant risk factors for POD. For male patients, preoperative anemia with Hb <13 g/dL was a significant risk factor for POD. This should be considered in the preoperative evaluation to detect patients at risk for POD and initiate preoperative measures to reduce the risk of POD. These include long-term glycaemic control of diabetic patients, reducing increased inflammatory activity, and correcting hypernatremia or anemia. Whether and to which extent these preoperative interventions are effective for the prevention of POD should be examined in further randomized, interventional studies.

AUTHOR CONTRIBUTIONS

Vera Guttenthaler: Conceptualization; methodology; writing—original draft; writing—review and editing. **Jacqueline Fidorra**: Investigation; writing—original draft; writing—review and editing. **Maria Wittmann**: Conceptualization; project administration; resources; supervision. **Jan Menzenbach**: Conceptualization; data curation; funding acquisition; methodology; project administration; supervision; validation; writing—original draft; writing—review and editing. All authors have read and approved the final version of the manuscript.

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Jan Menzenbach and Vera Guttenthaler designed the study protocol for the PROPDESC study. Jacqueline Fidorra participated in the data collection and analyzed the data. Vera Guttenthaler, Jacqueline Fidorra, and Jan Menzenbach prepared the manuscript. Andreas Mayr (University Bonn, Institute for Medical Biometry, Informatics and Epidemiology—IMBIE) provided statistical support. Maria Wittmann provided guidance throughout the design and conduction of the study and reviewed the manuscript. The authors would like to thank the PROPDESC study team for their dedicated work over 1 year to collect and document the abundant data. No sponsor participated in the design, methods, patient recruitment, data collection, analysis, or preparation of this manuscript. The PROPDESC study was funded by Funding Program Clinical Studies (FKS) of the Studienzentrum Bonn (SZB) at University Hospital Bonn (UKB) (Application: 2018-FKS-01/Grant: O-417.0002). The funder was not involved in the design of the study, collection, analysis, and interpretation of data, writing of the report, as well as the decision to submit the report for publication. Open Access funding enabled and organized by Projekt DEAL.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices) as well as the Study Protocol, are available immediately following publication, with no end date and for any purpose. Jan Menzenbach had full access to all of the data in this study and took complete responsibility for the integrity of the data and the accuracy of the data analysis.

TRANSPARENCY STATEMENT

The lead author, Jan Menzenbach, affirms that this manuscript is an honest, accurate, and transparent account of the study being reported, that no important aspects of the study have been omitted, and that any discrepancies from the study as planned (and if relevant, registered) have been explained.

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RESEARCH Open Access

Functional intervention following cardiac surgery to prevent postoperative delirium in older patients (FEEL WELL study)

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Abstract

Background Postoperative delirium is a common complication in patients after cardiac surgery, especially in older patients, and can manifest as a disturbance of attention and consciousness. It can lead to increased postoperative morbidity, prolonged need for care, and mortality. The presented study investigates whether the occurrence of postoperative delirium after cardiac surgery can be prevented by a multisensory stimulation. It was conducted as a prospective, randomized, controlled, non-pharmacological intervention study in the years 2021 and 2022 at the University Hospital Bonn in Germany. A total of 186 patients over 65 years with elective cardiac surgery were enrolled. Patients were randomized either to the intervention or control group. In both groups, postoperative delirium was assessed with the 3-min diagnostic interview for confusion assessment method on the first 5 days after surgery and pain was assessed using the Numeric Rating Scale. Multisensory stimulation was performed 20 min a day for the first three postoperative days in the intervention group.

Results The incidence of postoperative delirium was 22.6% in the intervention group and 49.5% in the control group ($p < 0.001$). Duration of postoperative delirium was significantly shorter in the intervention group ($p < 0.001$). Stay in the intensive care unit was significantly longer in the control group ($p = 0.006$). In the regression model non-intervention, high pain scores, advanced age, and prolonged mechanical ventilation were associated with postoperative delirium ($p = 0.007$; $p = 0.032$; $p = 0.006$; $p = 0.006$, respectively).

Conclusions Results of the study imply that a multisensory stimulation done on the first 3 days after planned cardiac surgery can reduce the incidence and duration of postoperative delirium in older patients. Influence of the treatment on the incidence of delirium in other patient groups, the length of stay in the intensive care unit, and patients´ postoperative pain should be confirmed in further clinical studies.

Trial registration: DRKS, DRKS00026909. Registered 28 October 2021, Retrospectively registered, https://drks.de/search/de/trial/DRKS00026909.

Keywords Cardiac surgery, Multisensory stimulation, Snoezelen, Older patients, Pain, Postoperative delirium

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Background

Postoperative delirium (POD) is a common phenomenon, especially in older patients after cardiac surgery, and is associated with increased morbidity and mortality [1–3]. Many predisposing and precipitating factors for the occurrence of POD after cardiac surgery have been identified. Chen et al. identified in a meta-analysis aging, diabetes, preoperative depression, mild cognitive impairment, carotid artery stenosis, NYHA functional class III or IV, time of mechanical ventilation, and length of intensive care unit stay as risk factors [4]. POD can lead to prolonged need for care, contributes to increased healthcare costs [5, 6] and can be distressing to both the patients and their families [7].

The incidence of delirium after cardiac surgery is reported in the range of 4.5–54.9% [4]. In a prospective study of postoperative delirium conducted in the year 2019 at the University Hospital in Bonn, Germany, a POD incidence of 50.0% was found in patients undergoing elective cardiac surgery in a sample size of 254 patients with a mean age of 70.5 years [8].

Due to its negative association with mortality, morbidity, as well as prolonged hospitalization, prevention of POD is of high importance. Because of the high rate of polypharmacy in older patients [9], it might be better for them to receive an alternative treatment for the prevention of POD. One of the non-pharmacological methods preventing delirium could be the Multisensory stimulation (MSS) so called *Snoezelen*.

Snoezelen was first introduced in the 1970s as an intervention for people with learning disabilities, based on the rationale of reducing the adverse effects of sensory deprivation. Over the time this application has been extended to the care of older people with dementia as both groups share some common characteristics, such as reduced cognitive functions and diminished communicative ability [10].

It creates gentle stimulations and a relaxing atmosphere that helps to reduce agitation and anxiety.

The characteristics of the *Snoezelen* are: (a) visual, auditory, tactile, and olfactory stimulation in a room or environment using lights, music, aromas, and tactile objects; (b) individual and non-directive intervention in which participants choose the sensory stimuli; (c) use of non-sequential and non-standardized stimulus; (d) reduced cognitive requirements [11].

The frequency of sessions varies from 3 sessions total to daily sessions over a 15-month period [10, 12–16].

Behavioural research in Alzheimer's disease and other dementing disorders drew the conclusion, that a person with impaired consciousness is particularly vulnerable to environmental influences [17] and that older people with dementia experience intrapsychic discomfort, because the rates of sense-stimulating and sense-soothing activities are imbalanced [18].

This might appear in hospitalized patients after surgery, due to an unfamiliar and often noisy environment ([19, 20].

The aim of the study was to evaluate whether a 20-min multisensory stimulation on postoperative days 1–3 could be used as an easy performable, non-pharmacological means to reduce the incidence of POD in older patients after elective cardiac surgery.

Methods

In this monocentric, prospective, randomized, controlled, non-pharmacological interventional study 237 patients that underwent elective cardiac surgery at the University Hospital Bonn from September 2021 until July 2022 were included. This study was carried out in accordance with the Helsinki Declaration. An ethics vote was provided by the Ethics Commitee of the Medical Faculty of the Rheinische Friedrich-Wilhelms-Universitaet Bonn (# 293/21). All consecutive patients older than 65 years with elective cardiac surgery were eligible if they were fluent in the German language, legally competent, and planned to be weaned from mechanical ventilation within 24 h after surgery (ınclusion criteria).

Exclusion criteria were emergency procedures, language barriers, documented severe psychiatric disorders or documented demantia. We excluded patients with a documented diagnosis of dementia, to minimize additional risk factors thought to be associated with delirium. To avoid the association between prolonged ventilation time and increased incidence of delirium, patients with an anticipated need for mechanical ventilation in the ICU for more than 24 h were also excluded. This patient group includes patients with severe respiratory comorbidities, that could lead to postoperative prolonged intubation, patients with preoperative respiratory failure or need for intubation and patients with a need for a left ventricular assist device (LVAD).

Written informed consent to the study was obtained from each patient before surgery. Then, patients were assigned to their respective groups (intervention group or control group) by lottery procedure.

Demographic and treatment data were collected by the study team from the anaesthesia protocols and the patient records. Patients were included consecutively over a period of 1 year and it is, therefore, anticipated, that both groups consisted of a comparable mix of cardiac surgical procedures.

Preoperative assessment, intraoperative handling, and postoperative treatment were performed the same in both groups according to the standard operating procedures of the University Hospital Bonn as only the study

personnel knew about the actual group assignment of the patient.

Upon arrival in the introduction suite pulse oximetry, electrocardiogram (ECG), and a peripheral and arterial line were established. Subsequently, anaesthesia was induced using sufentanil, propofol (1–1.5 mg/kg), and rocuronium (0.5 mg/kg). Following intubation, anaesthesia was maintained using sevoflurane at BIS values between 40 and 60, ensuring appropriate anaesthesia level. Next a central line and sheath were inserted into the right jugular venae under ultrasound guidance. Oxygen concentration was adjusted to maintain SpO_2 above 95%. Anaesthesia was maintained during surgery, including on-pump stages using sevoflurane and sufentanyl. At the end of surgery patients were transferred to ICU and extubated within 6 h after surgery according to current guidelines.

Postoperative treatment in the ICU was according to inhouse clinical standard and no intended differences between groups were made. In brief, patients were sedated with continuous infusions of propofol and sufentanil in the ICU during mechanical ventilation; neuromuscular blockade was not part of the regular regimen. Timing of extubation was left to the discretion of the attending physician who was blinded to patient study groups, according to the individual clinical course of the patient and whenever gas exchange was sufficient and patient was able to breath spontaneously and given hemodynamic stable situation, as well as when the patient reached normothermia. Additional clonidin was given in cases of shivering. Postoperative analgesia was regularly provided by piritramide as an individual bolus (2–5 mg) intravenously and additional metamizole intravenously as adjunctive analgesia when necessary or requested by the patient.

The day after surgery was defined as the first postoperative day. After the end of sedation and extubation with having a Richmond Agitation–Sedation Scale 0 or − 1 (RASS) [21], the 3-min diagnostic ınterview for confusion assessment method defined delirium (3D-CAM) was performed daily in the morning after routine medical treatments. Assessment continued from postoperative day 1 until day 5 and was scheduled to be finished before lunchtime. Testing was conducted by trained study personel in the ICU or the normal ward to detect a possible postoperative delirium in both groups. After the 5th day patients were no longer followed up as most incidences of POD happen in the first 5 days after surgery. It is assumed that, in accordance with the standard procedures of the ICU, no patients with delirium were discharged from ICU. The 3D-CAM can be completed in a median of 3 min, and has a sensitivity of 95% and specificity of 94% for detection of POD. The 3D-CAM is considered positive if acute onset or fluctuating course, inattention and either disorganized thinking or altered level of consciousness present according to the scoring system of the scale [22]. As the 3D-CAM test is not validated for patients on ICU, we set the sedation level for testing to a RASS score of 0 or − 1, which meant that patients were extubated and responsive. Acute pain was assessed postoperatively using the Numeric Rating Scale (NRS) at the time when patients were assessed for delirium [23]. Only the patients who were able to respond to the 3D-CAM test on a daily basis were asked to perform pain assessments with the NRS. The physicians who were responsible for the pain therapy were blinded to the *Snoezelen* treatment of the patient.

The intervention group received postoperative MSS treatment for three consecutive postoperative days. After lunchtime, patients, who were already extubated, were visited on ICU or the normal ward with a portable *Snoezelen* device with music system, projector, electronic candles, water column, scent machine and vibration pad on it. During the 20-min sessions, the room was darkened as much as possible and the patients listened to relaxing music according to their preference at a low volume and low pitch, and enjoyed the visuality that was created with light. The equipment consists of lighting effects such as electronic candles, illuminated water column and projector that can create different effects and images. The lights used were gentle, not flashing. All equipment was installed on a transportable device (Sinneswagen comfort+, Fa. Beluga, Germany). Depending on the patient's preference, aromatherapy scents and vibration cushion were also used. The practitioner who initiated the intervention left the patient alone for effective relaxation (Fig. 1).

The group of physicians and nurses who managed the care and treatment of the study patients, decisions on extubation, ward discharge, and analgesia applications were blinded to the study group.

Primary outcome was occurance of POD assessed in the ICU and the normal ward with the 3D-CAM. Secondary outcomes were length of stay in the ICU, length of stay in hospital, duration of delirium on postoperative days 1–5, and pain score after surgery assessed via NRS measuring the pain intensity from 0 to 10.

Statistics

We expected a relative reduction of POD in the intervention group by 40% through the intervention [24, 25]. A total sample size of at least 186 patients was required to have a power of 80% to detect a decrease in the primary outcome from 50% in the control group ($n=93$) to 30% in the experimental group ($n=93$) with a two-sided significance level of 5%.

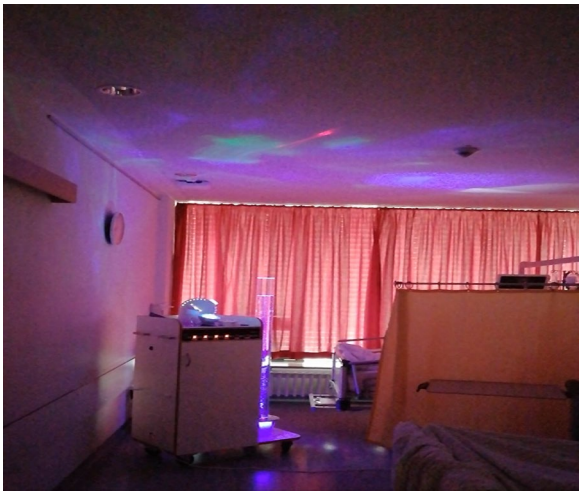

Fig. 1 Multisensorial stimulation treatment

The exploratory statistical analysis was performed using the statistical programming environment R. Continuous variables are presented with median and interquartile range (IQR). A normal distribution of the continuous variables was not present. Categorical variables are shown as numbers and percentages (%). The differences between intervention and control group regarding the characteristics were analyzed using the non-parametric Wilcoxon rank-sum test for continuous variables and the Fisher's exact test was computed to check for independence for categorical variables.

Logistic regression was performed to examine the effect of the intervention on POD development. POD entered the model as the binary outcome variable. Additional factors influencing POD were included as metric variables (ventilation time, NRS scores) or as categorical variables (age in increments of 5 years, The American Society of Anesthesiologists (ASA) classification and gender) and served as independent variables. The selected risk factors used in the logistic regression analysis represent accepted risk factors for development of postoperative delirium [5, 26, 27]. For better interpretability, (adjusted) odds ratios (OR) were generated via transformation from the regression coefficients and are reported with corresponding 95% confidence interval (CI).

Results

This study was conducted and reported in conformance with the CONSORT guidelines for randomised trials [28]. 289 Patients were enrolled to the study between September, 2021 and July, 2022.

Overall, 237 patients were randomised, of whom 125 were in the *Snoezelen* group, and 112 were in the control group. We included one new patient for every patient who dropped out of the study due to various reasons until we reached the number of 93 evaluable patients in each study group. 19 patients in the control group and 32 patients in the *Snoezelen* group were excluded from the study due to reasons, such as death, need for mechanical ventilation for > 24 h, cancellation of surgery, withdrawal of consent, and complications, such as bleeding requiring reoperation, acute cerebrovascular accident, and septic shock. 93 patients in each group were analysed (Fig. 2).

Patient characteristics and length of surgery were balanced among groups. The median age of the participating patients was 72 years. Age, proportion of male participants, ASA status, duration of surgery, grade of left ventricular ejection fraction, proportion of patients diagnosed with diabetes, and presence and severity of carotis artery stenosis did not differ significantly in the two study groups (Table 1). The Creatinine value and the estimated Glomerular Filtration Rate (eGFR) were comparable in both groups (Table 1). Of the 186 patients who participated in the study 137 were men. 98.3% of the patients were assigned to ASA physical status classification 3–4. No patient was in class ASA 1. 44.6% of all patients received preoperative oral midazolam for premedication (Table 1).

Patients stayed in the ICU for an average of 1–2 days after surgery. Duration of ICU stay differed significantly between the intervention and control group ($p = 0.006$) (Table 1). The median duration of mechanical ventilation after surgery in the ICU was significantly longer in the control group ($p = 0.014$) (Table 1). The median lenght of stay in hospital after surgery was 8 days and similar among both groups ($p = 0.673$) (Table 1). The total length of hospital stay was longer in the intervention group ($p = 0.045$) (Table 1).

The median duration of surgery in all patients was 166 min. Cardiac surgeries were classified as on-pump coronary artery bypass (CABG), off-pump coronary artery bypass, mitral valve surgery (MVR), aortic aneurysm surgery, aortic valve surgery (AVR) and complex surgeries (multiple valve replacement or combined bypass and valve replacement). There was no difference between the two groups regarding the types of operations (Table 2).

Numeric Rating Scale (NRS) scores for pain intensity were similar between the two groups in the first 3 days (Table 3). In both groups, pain scores decreased day by day and from the first day on mean NRS-scores were equal or less than 5 points. The pain scores in the intervention group were significantly lower on days 4 and 5 ($p = 0.022$; $p < 0.001$, respectively) (Table 3). On day 4, the 15 missing NRS-values included 4 missing values from the intervention group and 11 values from the control group (Table 3).

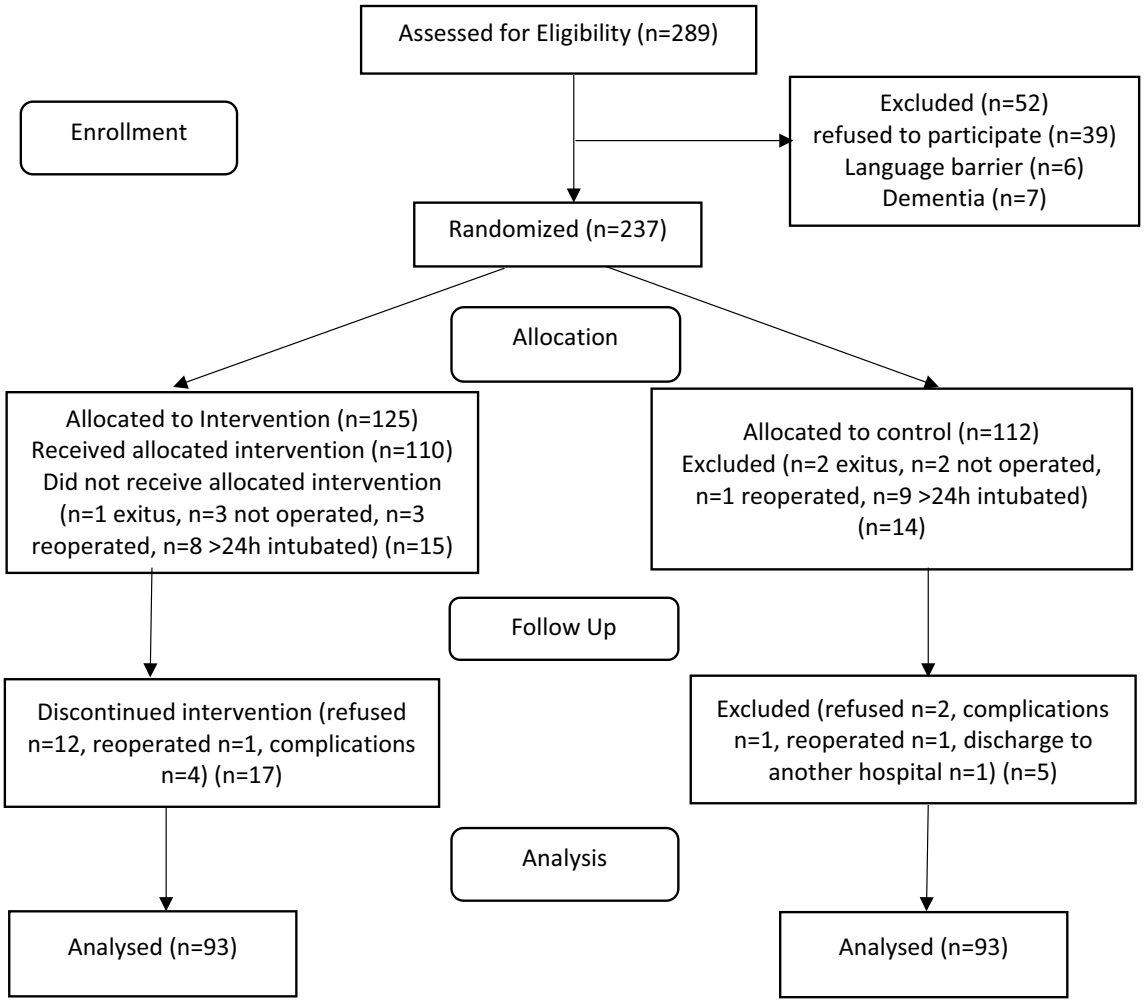

Fig. 2 Flow diagram of included patients

On day 5, there were 13 values missing from the intervention group and 15 from the control group (Table 3).

The incidence of delirium on postoperative days 1–5 was 22.6% (21 of 93) in the *Snoezelen* group (group S) and 49.5% (46 of 93) in the control group (group C) ($p < 0.001$) (Table 4). The length of delirium was significantly shorter in the *Snoezelen* group ($p < 0.001$) (Table 4). No patient in this group had delirium lasting longer than 4 days.

Although cardiac and respiratory values of the patients were not documented during the treatment, relaxation and restfulness were reported by most of the patients.

Logistic regression was performed to examine the effect of the intervention on POD development. Included factors were intervention, pain score on day 1 (NRS score), gender, ventilation time, age in increments of 5 years and ASA classification, and served as independent variables. Our regression model revealed that non-intervention (adj. OR 2.67), NRS score on day 1 (adj. OR 1.16), age (adj. OR 1.62) and ventilation time (adj. OR 1.12) were significantly associated with POD ($p = 0.007$; $p = 0.032$; $p = 0.006$; $p = 0.006$, respectively) (Table 5).

Discussion

In this prospective, randomized, controlled, non-pharmacological study, patients receiving a MSS intervention after elective cardiac surgery had a reduction of the delirium incidence by 54.4% which supports the hypothesis of the trial that the multisensory stimulation (so called *Snoezelen*) on postoperative days 1–3 may reduce the incidence of POD in this critically ill patient group. To the best of our knowledge, we did not encounter any studies in the literature that directly addressed the effect of *Snoezelen* treatment on POD. Some studies used music or bright light therapy, some of them used training of healthcare professionals on delirium awareness as intervention [5, 24, 25, 29–35]. The results were similar with ours. In the mHELP study Chen et al. also found a

Table 1 Demographics

	Total (*n* = 186)	Group S (*n* = 93)	Group C (*n* = 93)	*p* value	Missing
Age (years)				0.306	0
Median (IQR)	72 (69–77)	73 (69–77)	71 (69–76)		
Male, *n* (%)	137 (73.7%)	69 (74.2%)	68 (73.1%)	1.000	0
Duration of surgery (min)				0.134	5
Median (IQR)	166 (123–235)	179 (131.25–245.75)	157 (121–222)		
ASA-scores, *n* (%)				0.704	2
ASA 1	0	0	0		
ASA 2	1 (0.5%)	0	1 (1.1%)		
ASA 3	113 (60.8%)	56 (60.2%)	57 (61.3%)		
ASA 4	70 (37.6%)	37 (39.8%)	33 (35.5%)		
NYHA				0.713	16
1	25 (13.4%)	14 (15.1%)	11 (11.8%)		
2	74 (39.8%)	40 (43.0%)	34 (36.6%)		
3	71 (38.2%)	34 (36.6%)	37 (39.8%)		
Diabetes				0.234	0
Yes	140 (75.3%)	74 (79.6%)	66 (71.0%)		
Left ventricular ejection fraction				0.921	8
Highly reduced	3 (1.6%)	2 (2.2%)	1 (1.1%)		
Moderately reduced	16 (8.6%)	9 (9.7%)	7 (7.5%)		
Slighty reduced	50 (26.9%)	25 (26.9%)	25 (26.9%)		
Normal	109 (58.6%)	53 (57.0%)	56 (60.2%)		
Creatinine (mg/dl)				0.115	0
Median (IQR)	0.97 0.84–1.16)	0.93 (0.81–1.16)	1.00 (0.88–1.16)		
eGFR (ml/min)				0.443	1
15–29	2 (1.1%)	0 (0.0%)	2 (2.2%)		
30–59	48 (25.8%)	23 (24.7%)	25 (26.9%)		
60–89	110 (59.1%)	54 (58.1%)	56 (60.2%)		
≥ 90	25 (13.4%)	15 (16.1%)	10 (10.8%)		
Carotid artery stenosis				0.321	0
High-grade stenosis or occlusion	3 (1.6%)	0 (0%)	3 (3.2%)		
Moderate stenosis up to 70% right and left	12 (6.5%)	6 (6.5%)	6 (6.5%)		
Light stenosis up to 50% right and left	11 (5.9%)	4 (4.3%)	7 (7.5%)		
No hemodynamically relevant sclerosis	160 (86.0%)	83 (89.2%)	77 (82.8%)		
Midazolam as preoperative medication, *n* (%)				1.000	1
Yes	83 (44.6%)	42 (45.2%)	41 (44.1%)		
Length of ICU stay (hours)				0.006*	9
Median (IQR)	23 (20–46)	23 (19–30.75)	26 (21–68)		
Length of hospital stay after surgery (days)				0.673	0
Median (IQR)	8 (7–11)	8 (7–11)	8 (7–10)		
Length of hospital stay total (days)				0.045*	0
Median (IQR)	11 (9–15)	12 (10–17)	11 (9–14)		
Duration of mechanical ventilation in ICU (hours)				0.014*	8
Median (IQR)	0 (0–7.75)	0 (0–5.75)	3 (0–8)		

ASA American Society of Anaesthesiologist classification, *NYHA* New York Heart Association classification, *ICU* ıntensive care unit, *IQR* ınterquartile range, *eGFR* estimated glomerular filtration rate, *Group S* ıntervention group, *Group C* control group

*Significant with $p < 0.05$

Table 2 Type of cardiac surgery

	Total (*n* = 186)	Group S (*n* = 93)	Group C (*n* = 93)	*p* value	Missing
Type of Surgery				1.000	0
CABG (on-pump)	61 (32.8%)	30 (32.3%)	31 (33.3%)		
CABG (off-pump)	33 (17.7%)	17 (18.3%)	16 (17.2%)		
MVR	30 (16.1%)	13 (14%)	17 (18.2%)		
Aneurysm	4 (2.2%)	3 (3.2%)	1 (1.0%)		
AVR	22 (11.8%)	11 (11.8%)	11 (11.8%)		
Complex	36 (19.4%)	19 (20.4%)	17 (18.3%)		

CABG coronary artery bypass graft surgery, *MVR* mitral valve replacement, *AVR* aortic valve replacement, *Complex* CABG + MVR/AVR or multiple cardiac valve replacement, *Group S* ıntervention group, *Group C* control group

*Significant with $p < 0.05$

significant reduction of delirium incidence by 56% and a reduced hospital LOS of 2 days [36].

In our study the duration of delirium was shorter in the intervention group ($p < 0.001$). Milisen et al. could also shorten the duration of delirium in elderly hip-fracture patients by improving their nursing care and being aware of delirium in clinical practice [37].

The ASA scores were statistically similar between the groups but the percentage of ASA IV patients in the intervention group was higher. Although preoperative evaluation scores were worse, the length of ICU stay was shorter in our intervention group ($p = 0.006$). One component of this multifactorial situation may have been the positive effect of *Snoezelen* treatment on the recovery and well-being of patients. As shown in literature, non-pharmacological interventions, aimed at accelerating the recovery and well-being of patients, can shorten the duration of hospitalization which may also shorten the length of ICU stay as well [30, 33, 36].

The patient groups were determined by lottery in the preoperative period and the physicians making the extubation and treatment decision were blinded to the patient groups. However, the median duration of mechanical ventilation after surgery in the ICU was 0 h in the intervention group and 3 h in the control group, which was statistically significant ($p = 0.014$). Prolonged mechanical ventilation might be associated with prolonged intensive care admission and delirium [4, 27, 38]. This may be one of the reasons for prolonged stay in the ICU and increased delirium rates in the control group.

As a secondary outcome we investigated the length of stay in hospital after surgery, that was similar in both study groups ($p = 0.0673$). In older patients undergoing cardiac surgery, there are many factors other than delirium that influence length of hospitalization [39, 40].

Table 3 Numeric Rating Scale pain scores

	Total (*n* = 186)	Group S (*n* = 93)	Group C (*n* = 93)	*p* value	Missing
NRS score on day 1, median (IQR)	3 (1–5)	4 (1–5)	5 (0.3–5)	0.734	8
NRS score on day 2, median (IQR)	2 (0–5)	2 (0–4)	2 (0–6)	0.250	6
NRS score on day 3, median (IQR)	1 (0–4)	0 (0–3)	1 (0–5)	0.159	4
NRS score on day 4, median (IQR)	0 (0–3)	0 (0–2)	1 (0–4)	0.022*	15 (4:11)
NRS score on day 5, median (IQR)	0 (0–3)	0 (0–1)	1 (0–4)	< 0.001*	28 (13:15)

*Significant with $p < 0.05$

NRS Numeric Rating Scale, *Group S* ıntervention group, *Group C* control group, *IQR* ınterquartile range

Table 4 Duration of postoperative delirium

	Total (*n* = 186)	Group S (*n* = 93)	Group C (*n* = 93)	*p* value
Overall incidence of postoperative delirium, *n* (%)	67 (36.0%)	21 (22.6%)	46 (49.5%)	< 0.001*
Duration of delirium, *n* (%)				< 0.001*
POD on 1 day	25 (13.4%)	13 (14%)	12 (12.9%)	
POD on 2 days	11 (5.9%)	2 (2.2%)	9 (9.7%)	
POD on 3 days	13 (7.0%)	4 (4.3%)	9 (9.7%)	
POD on 4 days	9 (4.8%)	2 (2.2%)	7 (7.5%)	
POD on 5 days	9 (4.8%)	0 (0%)	9 (9.7%)	

Group S ıntervention group, *Group C* control group, *POD* postoperative delirium

*Significant with $p < 0.05$

Table 5 Regression model

	Adjusted odds ratio	95% confidence ınterval		*p* value
Ref. ınterventıon	2.67	1.32	5.53	0.007*
NRS score on day 1	1.16	1.01	1.33	0.032*
Ventilation time	1.12	1.03	1.21	0.006*
ASA-Scores	1.06	0.50	2.21	0.879
Gender	1.12	0.50	2.44	0.785
Age (increments of 5 years)	1.62	1.16	2.33	0.006*

NRS Numeric Rating Scale, *ASA* American Society of Anaesthesiologist classification

*Significant with $p < 0.05$

Therefore, this multifactorial outcome may not be altered significantly by correction of a single parameter.

Nevertheless, although this treatment does not shorten the length of hospitalization, it reduces the length of stay in the ICU. Since prolonged length of stay in the ICU is associated with serious complications, such as resistant infections etc., it is important to shorten this period [41].

In both groups, pain scores decreased day by day and from the first day on median NRS-scores were equal or less than 5 points, indicating that effective analgesia was achieved in both groups. We questioned pain scores daily during delirium assessment after routine medical treatments and before *Snoezelen* treatment. The pain scores were not significantly lower in the intervention group on days 1–3, but significantly lower on days 4 and 5 ($p = 0.022$; $p < 0.001$, respectively). Although there were many missing values in the pain assessment on the fifth postoperative day, the distribution of these missing values was similar between the groups. Many studies have shown that *Snoezelen* treatment reduces agitation and anxiety in target groups and increases well-being [10–16, 18]. The reduction of the pain scores after 3 times of *Snoezelen* could lead to the conclusion, that the intervention could reduce anxiety and improve the well-being of the patient which could lead to a decrease of the pain scores. As shown in many studies, high pain scores are associated with a higher incidence of perioperative delirium [41, 42]. It can be said that the incidence of delirium could also be reduced by reducing pain. However, although statistically different, the pain scores were low in both groups and it can be said the difference was not clinically significant.

Postoperative delirium is significantly associated with a raised mortality in hospital, as well as an increase in cognitive deficits of the patient. Patients experiencing a POD have an augmented need for nursing home care following hospitalization which enhances health care system costs [43–45]. Some studies have shown that general health expenditures increase up to 2.5 times in patients who have delirium compared to a similar population who does not have delirium [46, 47]. Considering the disadvantages that arise to patients and the health care system with the incidence of a postoperative delirium an intervention, such as *Snoezelen*, that necessitates relatively little effort and easy available equipment, might be a way to reduce raising health care costs. It could be a very cost-effective and affordable expenditure, if it could reduce the costs due to prolonged stay in the ICU, hospitalization, increased caregiver expenses, incidence of cognitive dysfunction and complications, such as delirium-related falls. The treatment also requires practitioners and time. However, the fact that the practitioner is only needed for the setup of the device and is not actively involved, reduces the time requirement. In addition, the time needed for MSS preparation should in general be less than the time needed to care for a hyperdelirious patient.

In our regression model, we found that non-intervention, NRS score on day 1, age and ventilation time were significantly associated with delirium. In other words, while high pain scores, prolonged ventilation time and advanced age increased delirium, the applied non-pharmacological intervention contributed to the prevention of delirium. These results are supported by the literature reviews [2, 3, 5, 31, 35, 36].

Limitations

Our study has some limitations:

(1) Although the sample size is large enough to meet the primary outcome it was a monocentric study with a relatively small number of patients.
(2) We are not able to prove in this study whether only *Snoezelen* treatment was effective or if there were other factors are involved. The reduction of POD incidence and duration could be due to the fact, that communication or interaction of any kind with the patient could prevent the occurrence of POD or shorten its length but it has to be considered, that all patients were visited during the testing period and communication was not limited to the intervention group. As only a limited number of concomittant parameters were assessed it could not be ruled out that other factors played a role in POD reduction, too.
(3) In our study, we used the 3D-CAM test to diagnose delirium. However, although this test is valid, it is not used as the gold standard test and is not validated for its use in the ICU. In addition, as patients were only tested once a day some patients with

delirium may have been missed due to its fluctuating course.

(4) We excluded patients with a documented diagnosis of dementia, to minimize additional risk factors thought to be associated with delirium but we did not assess dementia in our patients ourselves. Therefore, we might have included patients with an already existing mild cognitive impairment that could influence the occurance of POD. However, as we randomized our patients into two groups, the probability to have included patients with cognitive impairment is the same for both groups.

(5) We tried to keep the personnel on the wards blinded to the patient´s allocation to the respective study group. However, to minimize disruption during MSS treatment, the nurses were informed that the patient receives a study-related treatment without disclosing any study details and expected results. Therefore, the nurses were not completely blinded to the study.

Conclusions

As a result of extended human lifespans and aging populations POD is a growing and challenging health care problem and prevention, early diagnosis and treatment are of great importance.

Results of the study conducted on patients who underwent cardiac surgery imply that an individually composed multisensory stimulation done for 20 min on the first 3 days after surgery might be able to reduce the incidence and duration of postoperative delirium in older patients. A positive influence of the treatment on the incidence of delirium in other patient groups, patient´s length of stay in the intensive care unit, and postoperative pain should be confirmed in further clinical studies.

Abbreviations

ICU	Intensive care unit
POD	Postoperative delirium
DSM-V	Diagnostic and Statistical Manual of Mental Disorders 5th edition
mHELP	Modified Hospital Elder Life Program
MSS	Multisensory stimulation
LOS	Length of stay
AD	Alzheimers' disease
RASS Score	Richmond Agitation–Sedation Scale
3D-CAM	3-Minute Diagnostic Interview for Confusion Assessment Method
CAM–ICU	Confusion assessment method for ICU
NRS	Numeric Rating Scale
ASA	American Society of Anaesthesiology classification

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Author contributions

MW conceived of the presented idea, supervised and helped designing the project. TDD, VG and AZ designed the project; TDD, AZ, MOD and NK performed the interventions and tests; J-CS helped implementing the study in the intensive care unit. AK performed the statistical analysis of the data and wrote the statistical part of the manuscript; TDD and VG wrote the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data sets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Ethics vote for this study was provided by the Ethics Committee of the Medical Faculty of the Rheinische Friedrich-Wilhelms-Universitaet Bonn (# 293/21).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Original Contribution

PRe-Operative Prediction of postoperative DElirium by appropriate SCreening (PROPDESC) development and validation of a pragmatic POD risk screening score based on routine preoperative data

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ABSTRACT

Study objective: To develop and validate a pragmatic risk screening score for postoperative delirium (POD) based on routine preoperative data.
Design: Prospective observational monocentric trial.
Setting: Preoperative data and POD assessment were collected from cardiac and non-cardiac surgical patients at a German university hospital. Data-driven modelling approaches (step-wise vs. component-wise gradient boosting on complete and restricted predictor set) were compared to predictor selection by experts (investigators vs. external Delphi survey).
Patients: Inpatients (≥60 years) scheduled for elective surgery lasting more than 60 min.
Measurements: POD was assessed daily during first five postoperative or post-sedation days with confusion assessment method for intensive and standard care unit (CAM-ICU/CAM), 4 'A's test (4AT) and Delirium Observation Screening (DOS) scale.
Main results: From 1023 enrolled patients, 978 completed observations were separated in development ($n = 600$; POD incidence 22.2%) and validation ($n = 378$; POD incidence 25.7%) cohorts. Data-driven approaches generated models containing laboratory values, surgical discipline and several items on cognitive and quality of life assessment, which are time consuming to collect. Boosting on complete predictor set yielded the highest bootstrapped prediction accuracy (AUC 0.767) by selecting 12 predictors, with substantial dependence on cardiac surgery. Investigators selected via univariate comparison age, ASA and NYHA classification, surgical risk as well as 'serial subtraction' and 'sentence repetition' of the Montreal Cognitive Assessment (MoCA) to enable rapid collection of their risk score for preoperative screening. This investigator model provided slightly lower bootstrapped prediction accuracy (AUC 0.746) but proved to have robust results on validation cohort (AUC 0.725) irrespective of surgical discipline. Simplification of the investigator model by scaling and rounding of regression coefficients into the PROPDESC score achieved a comparable precision on the validation cohort (AUC 0.729).
Conclusions: The PROPDESC score showed promising performance on a separate validation cohort in predicting POD based on routine preoperative data. Suitability for universal screening needs to be shown in a large external validation.

1. Introduction

Postoperative delirium (POD) is the most common complication of older patients [1] aged 60 years and older, [2] occurring frequently within the first five days after surgery. [3–5] Incidences of POD range from 15 to 50% [6] and may increase up to 75% with prolonged ventilation during intensive care treatment. [7] Although appearing as a transient, early, postoperative complication with acute fluctuating

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disorders of consciousness, attention, perception and cognitive abilities., [8,9] POD may have lasting adverse effects on long-term outcome such as increased postoperative morbidity and mortality, prolonged hospital stay with higher treatment effort or persistent care dependency and cognitive decline. [1,10,11] With an estimated worldwide 2-fold increase of people over 65 by 2050 [12] and concurrently growing volume of surgical procedures, [13] POD is becoming an increasing challenge for healthcare systems.

Risk for POD is assumed to be determined by both patient-related predisposing factors and treatment-associated precipitating factors. Cognitive, sensory and functional impairments, multi-morbidity, polypharmacy and frailty are considered to be predisposing factors frequently related to ageing. [14] The resulting vulnerability is met by a second hit from precipitating factors such as surgery, pain, inflammation, exacerbation of chronic diseases and other external stressors or medication as triggers for POD. [1] Multifactorial pathogenesis of POD requires bundles of measures for prevention. Applying a modified Hospital Elder Life Program (mHELP), Chen et al. achieved a 56% reduction of POD within the intervention group versus control participants. [15] Considering limited resources of healthcare, these personnel- and cost-intensive efforts may have to be directed only at patients at increased risk. In order to focus prevention on patients at risk, routine screening for POD risk prior to surgery is essential and recommended by guidelines on postoperative delirium. [14,16]

In recent decades, several attempts have been made to build prognostic delirium risk models. Thus far, externally validated models [17] require extensive cognitive testing, functional assessments or laboratory values, and partly include further scores or data not available regularly prior to surgery. The resulting time consumption and preoperative lack of information hinder their implementation into clinical routine of surgical patients. Preoperative POD risk screening of older patients requires consistent applicability based on regularly available information. Thereby, a model composition of easy to asses variables supports universal use. [17] Moreover, adequate statistical processing [18,19] and standardised reporting on performance [20] in model development is demanded. To address this, model building requires both statistical and clinical input.

Aim of PROPDESC was to generate a universal pragmatic score based on preoperative data from patients of various surgical disciplines, which is easily applicable and thus can be implemented in clinical routine for preoperative POD risk screening. The PROPDESC score is intended to guide decision-making on preoperative POD-prevention in clinical application and to support further research on POD-management in scheduled trials.

2. Methods

2.1. Study design

PROPDESC is an investigator-initiated prospective monocentric observational trial conducted by the Department of Anesthesiology and Intensive Care Medicine at the University Hospital Bonn after approval by the Ethics Commission of the Medical Faculty of the Rheinische Friedrich-Wilhelms-Universität Bonn, Germany (application number 255/17). Participants were included after written informed consent during preoperative evaluation between 3rd September 2018 and 2nd October 2019. Preoperative data recording and patient testing were conducted in the anesthesia outpatient department and in the standard care wards. Postoperative assessment was performed in the intensive care and standard care units. Structured data and test results were entered pseudonymized (person-identifying data have been replaced by identification number) into an electronic database (REDCap), which was administered by the Institute for Medical Biometry, Informatics and Epidemiology at the University of Bonn.

In accordance with the study protocol, [21] 1097 patients were continuously included in PROPDESC. The first 600 patients with completed POD assessment constituted the development cohort to fit the risk model. Subsequent patients served as separate validation cohort to fairly evaluate its predictive performance. The definition of completed POD assessment required a valid conduct of at least three of the five scheduled postoperative visits to assess POD as primary outcome. Discharge to home before a third visit was accepted as exception to this rule, on the assumption that patients would not subsequently become delirious in their familiar environment. Therefore, these patients were rated as non-delirious unless they received a positive delirium diagnosis before their discharge. Patients who died during the 5-day visit period were rated as delirious if they presented POD prior to death. If they died without manifesting POD before completion of visit period, they were excluded from the analysis because it could not be ruled out that they could have developed POD during the study period.

2.2. Participants

Inpatients admitted to the Department of Anesthesiology for preoperative evaluation from cardiac and different non-cardiac surgical disciplines (orthopedics, thoracic, abdominal, vascular and others such as head, neck or mammary surgery) of the University Hospital Bonn were enrolled. Patients 60 years and older scheduled for elective surgery lasting more than 60 min were eligible (Inclusion criteria). Exclusion criteria were emergency procedures, language barriers and pre-existing mental retardation or severe dementia as determined by the physician, which constitute a lack of compliance to the study protocol by inhibiting adequate cognitive testing, delirium assessment and preclude contractual capacity to consent. [21]

2.3. Outcome

A positive POD diagnosis was considered if any of the applied assessment methods, specified below, detected POD at least once during the 5-day visit period. Delirium assessments were conducted every morning by trained study personnel on each of the first five days after surgery, or the first five days after the end of sedation. Sedated patients with Richmond Agitation-Sedation Scale (RASS) [22] score < -3 were considered as not assessable and therefore their testing for POD was initiated after exceeding this level of sedation according to CAM-ICU. [7,23] Application of various validated test instruments for POD assessment was distinguished for intensive care and standard care units. Confusion Assessment Method for ICU (CAM-ICU) was used for intensive care patients. Confusion Assessment Method (CAM) [24] and 4 'A's Test (4AT) [25] incorporating Alertness, Abbreviated Mental Test-4, Attention (Month Backwards test) and Acute change and fluctuating course were conducted on patients in standard wards. In order not to miss the diagnosis of delirium due to spot examination based on once-daily rounds by the study staff, the nurse in charge was queried at each visit about behavioural problems in the previous 24 h by using the 13-item Delirium Observation Screening Scale (DOS) [26] in addition to the above mentioned assessments. POD diagnosis was rated positive from a 4AT of 4 points or a DOS of 3 onwards. For each of the applied instruments, there is a risk of a type 1 error (false positive). Nevertheless, due to the known high number of undetected POD in clinical practice, this was judged to be less relevant than the risk of missing a POD diagnosis in terms of a type 2 error (false negative). Accuracy of POD assessment was promoted by extensive training of study staff and regular supervision by experienced physicians with expertise on POD for internal monitoring purposes. Study team members were instructed and trained in test administration prior to the start of the study. At the beginning of the study, a daily debriefing was conducted to clarify any questions that may have arisen during test performance. During the ongoing process of study implementation, a routine meeting with the study team was held once a month to discuss the progress of the study. Questions arising at short notice were clarified directly on site. Inclusion and assessment of patients for the validation cohort were conducted

continuously in the same manner as for the development cohort without information on statistical analysis in order to reduce detection bias.

2.4. Predictors

Preoperative data assessed by physicians of the Department of Anesthesiology during preoperative evaluation were collected and supplemented with cognitive testing and additional specific medical history by study personnel. Baseline characteristics included age, sex, body mass index (BMI), American Society of Anesthesiologists (ASA) Physical Status Classification System, Revised Cardiac Risk Index (rCRI), New York Heart Association Classification (NYHA), Metabolic Equivalent of Tasks (MET), surgical risk, surgical discipline, long-term medication, and preoperative laboratory values. To asses surgical risk the 5-level Johns-Hopkins classification [27] of intervention risk commonly used in the department was transformed into 3-level modified Johns Hopkins surgical criteria [28] similar to 3-level classification according to ESAIC guidelines [29,30] (adapted from Glance et al. [31]) for study purposes. In this process, 5-level Hopkins classes 1 and 2 were assigned to low-risk surgery, class 3 to intermediate-risk surgery, and classes 4 and 5 to high-risk surgery. [32]

In addition, study personnel performed the Montreal Cognitive Assessment (MoCA) [33] to detect pre-existing cognitive impairment. Subjective quality of life and physical function were assessed by the EQ-5D-5L and EQ-VAS [34,35]. Furthermore, preoperative assessable items of Kim's DELirium Prediction based on Hospital Information (DELPHI) score [36] were collected.

2.5. Sample size

Under the assumption of a POD incidence of about 30% in a mixed cohort of the university hospital and a required number of 10–20 events per variable (EPV) [37,38] to be estimated by a logistic regression model, the size of the development cohort was set to 600 patients. In order to obtain a reasonable number of events for the separate validation cohort, the planned sample size was set to at least 1000 patients.

2.6. Missing data

Frequencies of missing values are reported for all considered predictor variables and the outcome. For the bootstrap validation on the development cohort, we considered a complete case analysis to evaluate all considered models with the same sample size. For fitting the final model, only observations that had a missing value in one of the selected variables were excluded.

2.7. Statistical analysis methods

Statistical analysis was performed using the statistical programming environment R. For the description of the cohorts, continuous and ordinal variables are presented with mean and ± standard deviation (sd). Nominal variables are reported as numbers and percentages. Laboratory values are presented with median and inter-quartile range (IQR), due to the inherent skewness. Differences between the development and the validation cohort were analysed using the non-parametric Wilcoxon rank-sum test for continuous variables, and Fisher's exact test for categorical variables, considering a two-sided significance level of 0.05. For the first assessment of predictors, univariate logistic regression models were fitted with POD as outcome and the corresponding predictors as only explanatory variable. Odds-ratios from these models are reported, together with 95% confidence intervals (CI) and Likelihood-Ratio tests.

Different data-driven and subject-matter specific model building procedures were performed for risk score development. The resulting models were internally validated on the development cohort via bootstrapping (drawing 1000 bootstrap samples), therefore avoiding overoptimistic results like in classical internal validation. All modelling decisions were based solely on the performance in the bootstrap analysis. Afterwards, the finally selected model was estimated on the complete development cohort and subsequently evaluated on the separate validation cohort. Due to the non-random splitting of the data in development and validation cohort, this procedure can be considered as similar to an external validation. [39]

As evaluation criteria both in the bootstrap analysis on the development cohort and the quasi-external validation [39] on the validation cohort we considered the AUC (equivalent to the c-statistic) for the discriminatory power of the resulting models as well as the Brier Score (which additionally takes calibration into account).

After the final selection and estimation of the prediction model and its evaluation on the validation set, we additionally adapted the model to a simplified risk score via scaling and rounding of regression coefficients to the nearest integer. Subsequently, this simplified score was also validated on the validation cohort and its results are reported alongside the complete prediction model.

2.8. Model-building procedures

The study design included the collection of an extensive data set containing a large array of tests to explore and evaluate potential predictors to generate prognostic models. In collaboration between statisticians with expertise in statistical learning algorithms and experienced clinicians of investigators to provide clinical input, different prognostic models have been developed and analysed. In the comparison of different models the maximum achievable predictive accuracy of a comprehensive model was intended to be balanced against the applicability of a simplified risk score for clinical routine.

2.8.1. Step-wise model and boosting model

As purely data-driven model-building procedures we considered both a classical automated step-wise backward predictor selection (with the AIC criterion) [40,41] as well as a statistical learning algorithm (component-wise gradient boosting) [42] in combination with logistic regression. In both approaches, POD served as outcome, while all available predictors were considered as potential explanatory variables. The boosting approach originates from machine-learning and performs automated variable selection and regularization via gradient descent in function space in combination with early stopping. [43] As base-learners, we considered linear regression models for all continuous and categorical predictors. Tuning of the boosting algorithm was performed using 25-fold bootstrap on the considered training data. [44]

2.8.2. Restrictive boosting model

Since the aim of PROPDESC was to provide a feasible tool for POD prediction in clinical routine, an additional model was fitted on a restricted set of predictors containing only preoperative regularly available or easily obtainable parameters. For this purpose, laboratory values and the sum of MoCA test were excluded and the boosting approach was again performed on the restricted set of base-learners.

2.8.3. Investigator model

As a subject-matter strategy, investigators of PROPDESC selected predictive and easily obtainable parameters based on univariate comparisons in the development cohort and their assessment of feasibility to compose an investigator risk model for simple application in clinical practice.

2.8.4. Delphi survey model

Aspiring a more objective level of expert judgement on feasibility, to create a generally applicable and commonly adopted risk score, a Delphi expert survey was conducted to select variables collected by PROPDESC with regard to their expected prediction ability and feasibility in everyday practice. A panel of seventeen experienced clinicians from

several German hospitals with expertise on POD (as listed in acknowledgements) completed a two-stage Delphi survey as external experts without having information on descriptive and outcome statistics such as univariate logistic regression of the investigated PROPESC collective. In the first round, favoured parameters of the complete preoperative data set should be preselected by yes-no voting. The results of the first round were reported to the panel as reference for the second round. Based on this, parameters preselected by the first round were scored in terms of expected predictivity and feasibility in clinical practice using a five-level Likert scale. Additionally, a recommendation regarding the number of parameters included in their (Delphi survey) model was asked for.

3. Results

3.1. Participants

1097 eligible patients consented to participate in this observational study. The flow chart (Fig. 1) shows the case number of participants and their exclusion criteria. 72 patients did not undergo surgery for various reasons during the observation period. Another two patients withdrew their consent and were also considered as study dropouts. Of the remaining 1023 enrolled patients, 15 died during the 5-day visit period without manifesting POD. Since the completion of assessment for the primary endpoint of POD was not possible, these patients were also removed from the cohort. Additional 30 patients had less than three completed visits at the end of the study without having exhibited POD and were removed. However, patients who were discharged prior to a visit on the third day without manifesting POD before, were included as non-delirious on the assumption that they would not subsequently become delirious in their family environment. With this approach, 978 patients were included in the analysis.

The overall POD rate was 23.5% ($n = 230$). Baseline characteristics of the study collective are presented in Table 1. The total population had a mean age of 72.3 ± 7.3 years (38.3% women and 61.6% men). There were no significant differences in patient characteristics between the development and validation cohort.

Delirium incidence in the development cohort was 22.2% ($n = 133$) and 25.7% ($n = 97$) in the validation cohort. The highest incidence of delirium was observed after cardiac surgery procedures, with 52.0% in the development cohort. Table 2 shows the preoperatively collected variables for the non-POD and POD group of the development cohort. The delirious patients had a higher amount of continuous medication. Furthermore, the delirious patients had a higher mean troponin value and NT pro-BNP value preoperatively. On average delirious patients performed worse in risk assessments such as ASA, NYHA, rCRI, MET. In preoperative MoCA, delirious patients performed substantially lower than the non-delirious patients. Likewise, the delirious patients showed a lower Delphi [36] sum score. In terms of quality of life, non-delirious patients reported a higher score preoperatively.

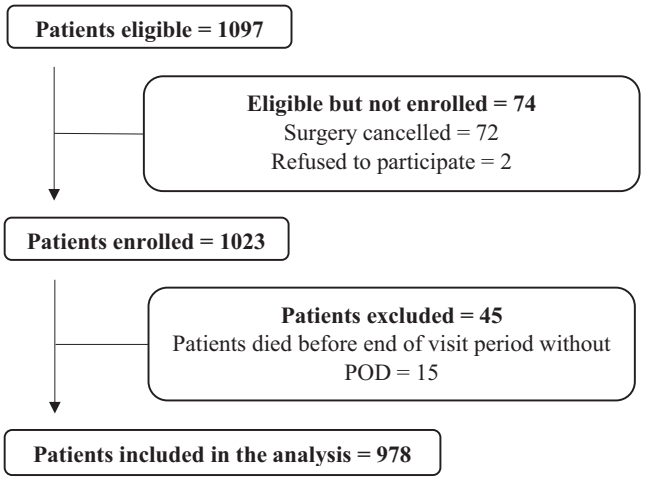

Fig. 1. Flow chart of patients in the PROPDESC cohort.

Table 1
Patient characteristics in relation to the development and validation cohort.

Characteristics	Total ($n = 978$)	Development cohort (n = 600)	Validation cohort (n = 378)	P value
Age (mean, sd)	72.3 ± 7.3	72.5 ± 7.2	71.9 ± 7.4	0.189
Sex				0.840
Female	375 (38.3)	232 (38.7)	143 (37.8)	
Male	602 (61.6)	368 (61.3)	234 (61.9)	
BMI (mean, sd)	27.7 ± 5.4	27.9 ± 5.6	27.4 ± 5.2	0.184
No. of medication (mean, sd)	6.0 ± 3.5	6.1 ± 3.5	5.7 ± 3.3	0.151
ASA				0.147
ASA 1	25 (2.6)	16 (2.7)	9 (2.4)	
ASA 2	339 (34.6)	224 (37.3)	115 (30.4)	
ASA 3	545 (55.7)	318 (53.0)	227 (60.1)	
ASA 4	69 (7.1)	42 (7.0)	27 (7.1)	
NYHA				0.917
NYHA I	413 (42.2)	252 (42.0)	161 (42.6)	
NYHA II	336 (34.4)	206 (34.3)	130 (34.4)	
NYHA III	212 (21.7)	130 (21.7)	82 (21.7)	
NYHA IV	17 (1.7)	12 (2.0)	5 (1.3)	
rCRI				0.531
rCRI 1	409 (41.8)	257 (42.8)	152 (40.2)	
rCRI 2	243 (24.9)	142 (23.7)	101 (26.7)	
rCRI 3	219 (22.4)	139 (23.2)	80 (21.2)	
rCRI 4	107 (10.9)	62 (10.3)	45 (11.9)	
MET				0.722
MET <1	11 (1.1)	5 (0.8)	6 (1.6)	
MET 1–4	459 (46.9)	284 (47.3)	175 (46.3)	
MET 5–10	475 (48.6)	290 (48.3)	185 (48.9)	
MET >10	33 (3.4)	21 (3.5)	12 (3.2)	

Data are number (%) unless stated otherwise. IQR = interquartile range, BMI = body mass index, ASA = American Society of Anesthesiology, NYHA = New York Heart Association, rCRI = Revised Cardiac Risk Index, MET = Metabolic Equivalent of Tasks. *P*-values refer to Wilcoxon tests for continuous variables and Fisher tests for categorical ones.

3.2. Model development and internal validation via bootstrapping

In the bootstrap analysis, the boosting approach selected prediction models containing on average 11 predictor effects (continuous variables or categorical effects) yielding a median AUC of 0.767 (Brier-Score: 0.142), while the classical step-wise procedure selected on average 8 variables yielding a median AUC of 0.737 and a Brier score of 0.152. Boosting on restricted predictor set (restricted boosting model) yielded a median AUC of 0.756 (Brier score of 0.144) and contained on average 16 predictor effects.

Selection of a variable set by investigators after univariate regression for a feasible clinical application resulted in a model compilation of age, ASA, NYHA, surgical risk, serial subtraction task (according MoCA on attention with maximum 3 points achievable) and repetition of two

Table 2
Predictors for POD for the development cohort, non-POD and POD group.

Predictors	Development cohort (n = 600)		P value	OR	CI (95%)	Missing data
	Non-POD	POD				
No.	467 (77.8)	133 (22.2)				
Age (mean, sd)	72.1 ± 7.2	73.8 ± 7.3	0.019	1.0	1.0–1.1	0 (0.0)
Sex			0.020			0 (0.0)
Female	192 (41.1)	40 (30.1)		Ref. = 1.0		
Male	275 (58.9)	93 (69.9)		1.6	1.1–2.5	
BMI (mean, sd)	28.1 ± 5.6	27.5 ± 5.3	0.303	1.0	0.9–1.0	2 (0.3)
No. of medication (mean, sd)	5.9 ± 3.6	6.7 ± 3.3	0.019	1.1	1.0–1.1	38 (6.3)
ASA			<0.001			0 (0.0)
ASA 1	15 (3.2)	1 (0.8)		Ref. = 1.0		
ASA 2	205 (43.9)	19 (14.3)		1.4	0.2–61.6	
ASA 3	223 (47.8)	95 (71.4)		6.4	1.0–271.5	
ASA 4	24 (5.1)	18 (13.5)		11.3	1.4–498.1	
NYHA			<0.001			0 (0.0)
NYHA I	223 (47.8)	29 (21.8)		Ref. = 1.0		
NYHA II	158 (33.8)	48 (36.1)		2.3	1.4–4.0	
NYHA III	79 (16.9)	51 (38.4)		5.0	2.9–8.7	
NYHA IV	7 (1.5)	5 (3.8)		5.5	1.3–21.4	
rCRI			<0.001			0 (0.0)
rCRI 1	232 (49.7)	25 (18.8)		Ref. = 1.0		
rCRI 2	113 (24.2)	29 (21.8)		2.4	1.3–4.4	
rCRI 3	86 (18.4)	53 (39.9)		5.7	3.2–10.2	
rCRI 4	36 (7.7)	26 (19.6)		6.7	3.3–13.5	
MET			0.002			0 (0.0)
MET <1	3 (0.6)	2 (1.5)		Ref. = 1.0		
MET 1–4	203 (43.5)	81 (60.9)		0.6	0.1–7.3	
MET 5–10	244 (52.3)	46 (34.6)		0.3	0.0–3.5	
MET >10	17 (3.6)	4 (3.0)		0.4	0.0–5.8	
Surgical discipline			<0.001			0 (0.0)
Others	112 (24.0)	13 (9.8)		Ref. = 1.0		
Cardiac surgery	73 (15.6)	79 (59.4)		9.3	4.7–19.5	
Orthopedics	192 (41.1)	28 (21.1)		1.3	0.6–2.8	
Thoracic surgery	8 (1.7)	2 (1.5)		2.2	0.2–12.5	
Abdominal surgery	70 (15.0)	7 (5.3)		0.9	0.3–2.5	
Vascular surgery	12 (2.6)	4 (3.0)		2.9	0.6–11.4	
Surgical risk			<0.001			0 (0.0)
Low	94 (20.1)	3 (2.3)		Ref. = 1.0		
Intermediate	234 (50.1)	46 (34.6)		6.2	1.9–31.6	
High	139 (29.8)	84 (63.2)		18.9	5.9–95.9	
Laboratory (median, (IQR))						
Haemoglobin (in g/dl)	13.6 (2.3)	13.3 (2.5)	0.124	0.9	0.8–1.0	0 (0.0)
Haematocrit (in %)	39 (7)	39 (7)	0.083	1.0	0.9–1.0	0 (0.0)
HbA1c (in %)	5.7 (0.7)	5.8 (0.9)	0.003	1.4	1.1–1.7	4 (0.7)
Leucocyte count (in G/l)	7.4 (2.6)	7.3 (2.4)	0.440	1.0	0.9–1.0	0 (0.0)
Sodium (in mmol/l)	140 (4)	140 (3)	0.885	1.0	0.9–1.1	0 (0.0)
Potassium (in mmol/l)	4.5 (0.5)	4.3 (0.5)	0.010	0.6	0.4–0.9	0 (0.0)
Creatinine (in mg/dl)	0.9 (0.3)	0.9 (0.4)	0.340	1.1	0.9–1.5	0 (0.0)
Total protein (in g/l)	69.4 (5.9)	69.5 (8.2)	0.137	1.0	0.9–1.0	5 (0.8)
C-reactive protein (in mg/l)	3.1 (6.9)	2.7 (7.3)	0.157	1.0	1.0–1.0	2 (0.3)
Troponin T (in ng/l)	10.8 (11.9)	16.2 (19.0)	<0.001	1.0	1.0–1.0	0 (0.0)
NT pro-BNP (in pg/ml)	165.0 (363.8)	367.5 (849.3)	0.052	1.0	1.0–1.0	21 (3.5)
Validated scores (mean, sd)						
Delphi Score sum	4.3 ± 2.1	6.1 ± 1.6	<0.001	1.6	1.4–1.8	0 (0.0)
EQ-5D-5L						
Mobility	2.4 ± 1.4	2.1 ± 1.4	0.063	0.9	0.8–1.0	0 (0.0)
Self-care	1.5 ± 0.9	1.4 ± 1.0	0.902	1.0	0.8.1.2	1 (0.2)
Usual activities	2.0 ± 1.3	1.9 ± 1.3	0.385	0.9	0.8–1.1	0 (0.0)
Pain/discomfort	2.6 ± 1.3	2.2 ± 1.2	0.002	0.8	0.7–0.9	0 (0.0)
Anxiety/depression	1.7 ± 1.0	1.7 ± 1.1	0.498	1.1	0.9–1.3	2 (0.3)
EQ-VAS	61.6 ± 22.2	58.8 ± 23.3	0.218	1.0	1.0–1.0	3 (0.5)
MoCA sum	23.3 ± 3.8	21.8 ± 4.2	<0.001	0.9	0.9–1.0	0 (0.0)
Trail making test	0.6 ± 0.5	0.5 ± 0.5	0.021	0.6	0.4–0.9	4 (0.7)
Copy cube	0.5 ± 0.5	0.4 ± 0.5	0.398	0.8	0.6–1.2	4 (0.7)
Clock drawing	2.4 ± 0.8	2.3 ± 0.9	0.064	0.8	0.6–1.0	4 (0.7)
Naming animals	2.9 ± 0.3	3.0 ± 0.2	0.157	1.8	0.8–4.9	2 (0.3)
Repeating numbers	1.7 ± 0.6	1.5 ± 0.6	0.051	0.7	0.5–1.0	0 (0.0)
Letter attention	0.9 ± 0.3	0.8 ± 0.4	0.121	0.7	0.4–1.1	0 (0.0)
Subtraction	2.8 ± 0.6	2.6 ± 0.8	0.008	0.7	0.5–0.9	0 (0.0)
Sentence repetition	1.5 ± 0.7	1.3 ± 0.8	0.017	0.7	0.6–0.9	1 (0.2)
Fluency language	0.4 ± 0.5	0.3 ± 0.4	0.020	0.6	0.4–0.9	1 (0.2)
Abstraction	1.1 ± 0.8	1.0 ± 0.8	0.395	0.9	0.7–1.1	0 (0.0)
Memory	2.4 ± 1.6	1.8 ± 1.6	<0.001	0.8	0.7–0.9	0 (0.0)
Orientation	5.9 ± 0.6	5.8 ± 0.6	0.234	0.8	0.6–1.1	0 (0.0)
Education level	0.4 ± 0.5	0.5 ± 0.5	0.138	1.3	0.9–2.0	1 (0.2)

Data are number (%) unless stated otherwise. IQR = interquartile range, POD=Postoperative delirium, OR = Odds Ratio, CI=Confidence Interval, Ref. = Reference, BMI = body mass index, ASA = American Society of Anesthesiology, NYHA = New York Heart Association, rCRI = Revised Cardiac Risk Index, MET = Metabolic Equivalent of Tasks, MoCA = Montreal Cognitive Assessment. p-values refer to Likelihood-Ratio test on univariate logistic regression models with POD as outcome and the corresponding predictor as only explanatory variable.

syntactically complex sentences (according MoCA on language with maximum 2 points achievable). This investigator model achieved a slightly lower bootstrapped median AUC of 0.746 (Brier-Score: 0.150).

As consensus of the Delphi survey among external experts, without having information on descriptive or statistical data of the PROPDESC collective, an average model size of seven parameters was preferred. In total, 16 variables (listed in Supplementary Table 1) received at least 60% agreement in the first survey round. Their rating results for predictivity and feasibility by a five-level Likert scale in the second survey round are also shown in Supplementary Fig 1 of the supplements. The seven best rated variables were compiled into a model. This Delphi survey model achieved a median AUC of 0.582 (Brier-Score of 0.170) in the internal bootstrap analysis.

An overview on the different considered prediction models and their coefficients from logistic regression, fitted on the complete development cohort, is displayed in Supplementary Table 2 of the supplements.

3.3. Model specification

The different AUC and Brier scores from internal bootstrap validation show that the boosting model is estimated to perform best in terms of POD prediction (Table 3). Nevertheless, due to the expected better applicability in clinical routine with easy to collect variables and low time consumption, the investigator model was chosen as the final model accepting a moderate decrease in AUC and a slightly higher Brier score. Since the PROPDESC risk score is not only intended to be applicable in university hospitals with cardiac surgery, internal validation was also performed for the subgroup without cardiac surgery. The AUC drops slightly when excluding patients with cardiac surgery. This decrease in AUC with respect to non-cardiac patients was the smallest for the investigator model compared to the other models (Table 3).

3.4. Final model and performance on validation cohort

The final model (investigator model) yielded an AUC of 0.725 (Brier score = 0.172) on the validation cohort (Table 3, Fig. 2), therefore showing a slightly lower performance on a completely separate cohort compared to the internal bootstrap validation. The coefficients for the final model are presented in Table 4. Predicted probabilities for individual patients can be computed by:

$$1/(1+exp(-(\,7.8168+0.0456\,Age\;[years]+0.4619\,ASA\;[points]+0.3842\,NYHA\;[points]+1.8894\;[if\;surgery\;risk\;is\;intermediate]$$
$$+2.7734\;[if\;surgical\;risk\;is\;high]-0.2731\,MoCA\;repetition\;of\;sentences-0.2376\,MoCA\;serial\;subtracing\;)\,)\,).$$

The simplified "bedside" risk score is calculated by summing up 1 point per year, 10 points each per class of ASA and NYHA, 40 points for intermediate or 60 points for high surgical risk and finally subtracting 5 points for each point achieved on MoCA items (Table 4). The simplified score showed a very similar performance (AUC = 0.729, Fig. 2) on the validation cohort. The corresponding probabilities for a new patient regarding different score levels can also be derived from Table 4. The performances on a subsample without cardiac surgery were nearly identical with an AUC = 0.724 for the complete prediction model and AUC = 0.722 for the simplified score.

4. Discussion

4.1. Principle findings

We developed and validated a prognostic model for POD based on a comprehensive preoperative dataset. The PROPDESC score estimates POD risk based on age, ASA physical status, NYHA classification, operative risk and short cognitive assessment (serial subtraction task and repetition of two syntactically complex sentences) according to MoCA on attention and language. Important features of the instrument are rapid and ready preoperative availability of required parameters as recommended by guidelines on postoperative delirium. [14]

4.2. Strengths and weaknesses of the study

The final PROPDESC model was composed aiming for feasibility by investigators based on univariate comparisons in the development cohort. The investigator model compiled in this way (containing 6 variables) performed just slightly below purely data-driven statistical learning procedures with respect to prediction accuracy via bootstrapping on development cohort (median $AUC_{investigator}$ of 0.746 vs. median $AUC_{boosting}$ of 0.767). Boosting approaches provided models with the highest prediction accuracy, but consisted of more variables (12 to 16) and, in particular, contained more cognitive tests or patient surveys which have to be collected additionally to routine. Furthermore, PROPDESC included a notable proportion of cardiac surgery patients with a POD incidence considerably above average of total collective. Thus cardiac surgery contributed substantially to prognostic power in purely data-based models. The predictive power of the investigator

Table 3
Results from the bootstrap analysis on the development cohort for all considered prediction models as well as the results on the validation cohort for the final prediction model (investigator model) and the simplified score. The Brier score can only be computed for the probabilistic models, and not the simplified score. For sensitivity reasons, validation was also performed on a cohort without cardiac surgeries (AUC non-cardiac).

Bootstrap analysis on Development Cohort	*AUC (median)*	*Range (min–max)*	*Brier score (median)*	*Range (min–max)*	*AUC non-cardiac surgery (median)*	*Range (min–max)*
Boosting model	0.767	0.649–0.854	0.142	0.128–0.185	0.643	0.417–0.826
Restrictive boosting model	0.756	0.636–0.850	0.144	0.129–0.178	0.631	0.387–0.793
Step-wise model	0.737	0.563–0.843	0.153	0.121–0.196	0.620	0.425–0.798
Delphi survey model	0.581	0.408–0.715	0.170	0.160–0.197	0.598	0.440–0.774
Investigator model	0.746	0.633–0.855	0.150	0.131–0.179	0.661	0.393–0.846
Validation cohort	*AUC*	*95% CI*	*Brier score*	*95% CI*	*AUC non-cardiac surgery*	*95% CI*
Prediction model (Investigator model)	0.725	0.672–0.777	0.172	0.151–0.193	0.724	0.648–0.798
Simplified score	0.729	0.677–0.782	–	–	0.722	0.647–0.798

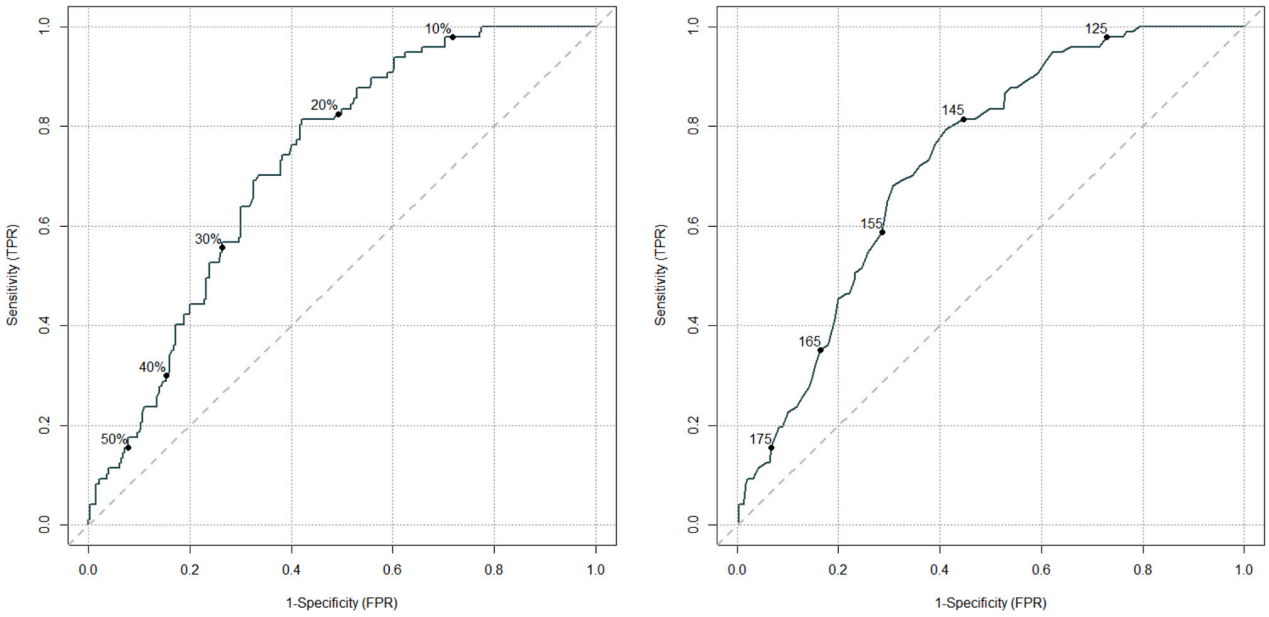

Fig. 2. Receiver-Operator-Characteristics (ROC) Curves for the final prediction model (left) and the simplified score (right) on validation cohort. Potential cutpoints for risk-stratification are displayed as individual percentages for final prediction model (left) and as total score points for simplified score (right).

Table 4
Coefficients for the final prediction model (investigator model) estimated via logistic regression on the development cohort and a simplified score (derived via scaling and rounding of coefficients).

Variables	Coefficients	Simplified score
Intercept	−7.8168	
Age	0.0465	Age (in years)
ASA Classification	0.4619	+ 10 * (result of ASA class)
NYHA Classification	0.3842	+ 10 * (result of NYHA class)
Surgical risk intermediate	1.8894	+ 40 [if surgical risk = intermediate]
Surgical risk high	2.7734	+ 60 [if surgical risk = high]
Serial subtracting (MoCA)	−0.2376	− 5 * (result of subtracting)
Repetition of two sentences (MoCA)	−0.2731	− 5 * (result of repetition of sentences)
Simplified score rating and corresponding POD risk	*Rating*	*POD risk*
	<125 points	<10%
	125–144 points	10–20%
	145–154 points	20–30%
	155–164 points	30–40%
	165–174 points	40–50%
	≥175 points	>50%

ASA = American Society of Anesthesiology, NYHA = New York Heart Association, MoCA = Montreal Cognitive Assessment, POD=Postoperative Delirium.

model proved robust on the separated validation cohort, irrespective of surgical discipline (AUC_{total} 0.725 vs. $AUC_{non\text{-}cardiac}$ 0.724). The simplified bed-side score of this investigator model showed a comparable AUC of 0.729 on that validation cohort.

4.3. Key principles for model development

Key principles for development of a prognostic model on POD risk include (1) to sample a sufficient number of patients, (2) to investigate a comprehensive data set of preoperative information addressing multifactorial genesis of POD and (3) to provide sensitive detection of primary endpoint, as missing POD diagnosis in clinical practice is likely high.

(1) Number of patients with positive POD diagnosis in the development cohort (n = 133) results in an EPV of 1:22 on 6-paramater PROPDESC score. Lindroth et al. demand just an EPV of at least 1:10 to avoid statistical overfitting, which could impair validation. [17]

(2) PROPDESC score accounts for risk components of different etiologies by factoring age, comorbidity, functional status, surgical invasiveness and cognitive performance.

(3) POD assessment was conducted on the first five days after surgery or end of sedation. This is considered the interval with highest probability of POD occurrence, according to the literature. Study staff performed daily examinations (including weekends) with validated instruments. These spot checks were supplemented by DOS survey of nursing staff to avoid missing POD.

4.4. Comparison to other studies

Despite the effort to compare several different modelling approaches including complex machine learning algorithms, the models in this study did not reach a comparably high predictive accuracy as the best model (AUC = 0.94) [36] reported in a meta-analysis. [17] However, Kim conducted enrolment partly after POD onset in his Delphi trial and also involved data not available prior to surgery for development of his prediction model. [36] Further models [17] provided a comparable AUC to PROPDESC score, but relied on information of extensive cognitive testing not applicable as preoperative routine.

Intending to develop a compact predictive model, Lindroth et al. developed a so-called two-factor model. [45] However, these factors are the NSQIP-SC score, which consists of 21 preoperative parameters including the Current Procedural Terminology (CPT) code out of 1557 unique codes in combination with the Trail making test B (TMTB). Since the NSQIP-SC is not automatically available pre-operatively in every country and the TMTB requires a paper sketch and the ability to draw, this construct does not seem to be suitable as rapid assessment for clinical routine and preoperative bedside screening. Furthermore, the achieved predictive accuracy with an AUC of 0.81 was determined in an analysis of only 97 patients. Enhancing the American College of Surgeons NSQIP Surgical Risk Calculator to predict the geriatric-specific outcomes “pressure ulcer, delirium, new mobility aid use, and

functional decline", it was supplemented by 6 additional parameters to the previous 21. Thus, it seems unsuitable for rapid patient-side application during preoperative evaluation as well. [46]

A recently published study [47] with a comparable number of cases to PROPDESC, was limited to abdominal surgery patients and also considered postoperative status as surgical APGAR (sAPGAR) [48] in addition to preoperative risk factors for POD prediction. Li et al., similarly to PROPDESC, did not include patients with pre-existing dementia, delirium, or disorders of consciousness in their trial. [47]

In order to screen a patient collective for POD risk, the entire sample should be evaluated for detecting patients at risk. A complex risk score with a slightly higher precision does not provide a better screening efficacy if it is not routinely applicable and thus many patients remain unassessed Aiming to develop a screening tool, we prioritised the simpler applicability of the investigator model over the highest accuracy of the boosting model, which is rather required for diagnostic tools. Predictive power and rapid assessment of the PROPDESC score is expected to enable decision making on POD prophylaxis in clinical routine. For example, despite an AUC_{mean} of 0.69, preoperative APFEL score for estimating the risk of postoperative nausea and vomiting (PONV) has proven useful for decision making on PONV prophylaxis because of simple handling in clinical practice. [49]

The PROPDESC score is intended for risk screening in clinical use and future research. If the score indicates an increased risk by the collected risk factors (age, ASA, NYHA, operative risk), cognitive testing (subtracting points for MoCA on attention and language, see Table 4) gains particular importance for decision-making in clinical practice. As model development and internal validation of PROPDESC were conducted in a monocentric setting, external multicentre validation is scheduled to confirm universal applicability.

4.5. Limitations

Limitations of the PROPDESC trial are the exclusion of patients with emergency procedures, language barriers and pre-existing mental retardation or severe dementia as determined by the physician. Consequently, on the one hand, these conditions were not considered as risk factors for POD when developing the score. On the other hand, they would have hindered adequate performance of pre- and postoperative cognitive assessments, as well as valid differentiation between pre-existing mental disorders and acute onset during POD.

The gold standard for diagnosing delirium would be an extensive examination by a psychiatrist, which however is usually not feasible in clinical routine of surgical patients. Therefore, POD assessment of this trial was also limited to the five-day assessment described above.

Another limitation to be mentioned is that although this study carefully separated development and validation cohort, one can still not rule out some overfitting and overoptimism in the validation as both cohorts were derived from the same hospital.

4.6. Conclusions

POD risk screening as recommended by guidelines on postoperative delirium [14] is intended to guide decision-making on preventive management in clinical practice. This study developed a risk score based on statistical and clinical input in a monocentric observational trial on older inpatients (≥60 years) from various surgical disciplines. The proposed PROPDESC score showed a good prediction accuracy irrespective of surgical discipline but requires only a short time to collect preoperative available parameters. This seems promising as universal risk screening tool, but demands subsequent external validation.

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Ethical approval

The work described has been carried out in accordance with the Declaration of Helsinki (Code of Ethics of the World Medical Association for experiments involving humans). Research ethics board approval was obtained by the Ethics Commission of the Medical Faculty of the Rheinische Friedrich-Wilhelms-Universität Bonn, Germany (Chairperson Prof K. Racké; application number 255/17).

Study design

The study protocol including amendments was finalized on 2nd of May 2018 as version 2.1. and has been published (org/10.1016/j.conctc.2019.100501). [21]

Study registration

This study was registered in the German Clinical Trials Register/ Deutsches Register Klinischer Studien (DRKS-ID: DRKS00015715).

Data sharing

The data generated and/or analysed during PROPDESC trial are available from the corresponding author on reasonable request.

Author contributions

Jan Menzenbach, Maria Wittmann and Vera Guttenthaler have substantially contributed to the interpretation of current specific knowledge, which resulted in the conception and design of the present trial. Jan Menzenbach, Andrea Kirfel, Andreas Mayr and Maria Wittmann are responsible for data clearing, for strategies of model development and for interpretation of results. Jan Menzenbach is sponsor and principle investigator of the present trial and participated in the acquisition of funding. Jan Menzenbach and Andrea Kirfel wrote the manuscript, revised it critically for important intellectual content, and approved the final manuscript. Vera Guttenthaler co-authored the manuscript.The study team consisted of physicians and non-physicians from the Clinic for Anesthesiology at the University Hospital of Bonn as well as doctoral students who were supervised by Maria Wittmann and Jan Menzenbach. PROPDESC Collaboration Group contributed to the data collection and external experts who participated in the Delphi survey are listed in the acknowledgements. Andrea Kirfel, Jan Menzenbach and Maria Wittmann are responsible for project management. Andreas Mayr and Christian Staerk wrote the statistical methods. Arcangelo Ricchiuto was responsible for the building, management and backup of the REDCap database. Statistical processing of the study data was supported and performed by the Institute for Medical Biometry, Informatics and Epidemiology (IMBIE) at the University of Bonn supervised by Andreas Mayr. Mark Coburn and Maria Wittmann supervised the score development and critically reviewed the manuscript. All authors read and approved the final manuscript.

Author contributions

Jan Menzenbach, Maria Wittmann and Vera Guttenthaler have substantially contributed to the interpretation of current specific knowledge, which resulted in the conception and design of the present trial. Jan Menzenbach, Andrea Kirfel, Andreas Mayr and Maria Wittmann are responsible for data clearing, for strategies of model development and for interpretation of results. Jan Menzenbach is sponsor and principle investigator of the present trial and participated in the

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Declaration of Competing interest

Competing interests: none

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jclinane.2022.110684.

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PROPDESC-Score-Validierung (PROPDESC-Val)

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Hintergrund und Hypothesen

Das postoperative Delir (POD) ist eine der häufigsten Komplikationen nach chirurgischen Eingriffen bei älteren Patienten mit einer Inzidenz von 11–51 % [1, 2]. Obwohl das POD als frühe, vorübergehende, postoperative Komplikation auftritt, kann es zu schwerwiegenden langfristigen Verschlechterungen führen, wie z. B. zu erhöhter Sterblichkeit, zu anhaltenden kognitiven Beeinträchtigungen sowie zur Einschränkung der Mobilität und der Selbstständigkeit [3]. Neben dem Alter und der Multimorbidität stellen sensorische, funktionelle und kognitive Beeinträchtigungen ein erhöhtes Risiko für POD dar [4]. Trotz der potenziell schwerwiegenden Schäden für die Patienten und der Belastung der Gesundheitsressourcen gibt es derzeit kein standardisiertes POD-Risiko-Screening in deutschen Krankenhäusern, obwohl auch die European Society of Anaesthesiology and Intensive Care (ESAIC) die Relevanz einer präoperativen Identifizierung von POD-Risikopatienten betont und sie zu einem Eckpunkt ihrer Leitlinie zum POD macht [3]. Die präoperative Vorhersage des POD-Risikos von Patienten bietet die Möglichkeit, Hochrisikopatienten rechtzeitig zu erkennen, um vorbeugende Maßnahmen einzuleiten. Chen et al. haben gezeigt, dass die im Modified Hospital Elder Life Program (mHELP) beschriebenen Maßnahmen das Auftreten des POD um 56 % reduzieren konnten [5].

Es gab einige Versuche, einen Risikoscore zur POD-Risiko-Detektion zu entwickeln, z. B. von Inouye et al. [6] und Kim et al. [7, 8], diese verwenden jedoch Parameter, die im Allgemeinen beim Prämedikationsbesuch nicht verfügbar sind. In den PROPDESC(Pre-Operative Prediction of Postoperative Delirium by Appropriate Screening)-Score [9] werden präoperativ verfügbare Ausgangsparameter einbezogen, ergänzt durch 2 sehr kurze kognitive Testfragen. Ziel von PROPDESC-Val (PROPDESC Score Validation) ist es, den intern am Universitätsklinikum Bonn entwickelten und validierten Score in unterschiedlichen Krankenhäusern Deutschlands extern als präoperatives POD-Risiko-Screening zu validieren.

Details der Studie

PROPDESC-Val ist eine multizentrische, observatorische, investigatorinitiierte, prospektive Validierungsstudie, die in Krankenhäusern aller Versorgungsstufen in Deutschland durchgeführt wird (Einschlusskriterien: Alter ≥ 60 Jahre; mind. 1-stündige elektive Operation, geplanter stationärer Aufenthalt in der Nacht nach der Operation, unterschriebene Ein-

Infobox 1

Link zur Studienbeschreibung der DGAI
https://www.dgai.de/forschung-preise/dgai-studienzentrum/dgai-gefoerderte-multizenterstudien.html

Zusatzmaterial online

Die Online-Version dieses Beitrags (https://doi.org/10.1007/s00101-023-01371-4) enthält eine vollständige Liste aller Studienzentren.

QR-Code scannen & Beitrag online lesen

Tab. 1 Studienablauf

	Visite 0	Visite 1	Visite 2	Visite 3	Visite 4	Visite 5	Entlasstag
	Screening	1. postop. Tag	2. postop. Tag	3. postop. Tag	4. postop. Tag	5. postop. Tag	
Ein-/Ausschlusskriterien	x	–	–	–	–	–	–
Demographische Daten	x	–	–	–	–	–	–
Einwilligung	x	–	–	–	–	–	–
PROPDESC-Score	x	–	–	–	–	–	–
Delirtest	–	x	x	x	x	x	–
Operationsdaten	–	x	–	–	–	–	–
Dauer des Krankenhausaufenthalts	–	–	–	–	–	–	x

postop. postoperativ, ***PROPDESC*** Pre-Operative Prediction of Postoperative Delirium by Appropriate Screening

willigungserklärung; Ausschlusskriterien: Patienten mit Sprachbarrieren, neurochirurgische Eingriffe, Betreuung, Demenz, Teilnahme an interventioneller POD-Studie; primärer Endpunkt: Validierung des PROPDESC-Scores in deutschen Krankenhäusern; sekundäre Endpunkte: Auswirkungen des POD auf die Dauer des Krankenhausaufenthalts und die Sterblichkeit im Krankenhaus). Zudem wird der Einfluss der Selbstversorgung, des präoperativen Alkoholkonsums und der Lagerung während der Operation auf das Auftreten eines POD untersucht.

Die Patienten werden an den ersten 5 Tagen nach der Operation vormittags mit CAM-ICU (Confusion Assessment Method for the Intensive Care Unit) auf der Intensivstation und mit 3D-CAM (3-Minute Diagnostic Interview for CAM-defined Delirium) auf Normalstation auf POD getestet (◘ **Tab. 1**).

Mitwirkung

Es werden weiterhin Krankenhäuser aller Versorgungsstufen in Deutschland gesucht. Falls Sie Interesse an der Mitarbeit bei PROPDESC-Val oder Fragen zur Studie haben, melden Sie sich gerne bei Prof. Dr. Maria Wittmann (Maria.Wittmann@ukbonn.de) oder Vera Guttenthaler (Vera.Guttenthaler@ukbonn.de).

Statistik

Die Fallzahlberechnung basiert auf den Ergebnissen der PROPDESC-Studie. Die POD-Inzidenz lag hier bei gleichen Ein- und Ausschlusskriterien insgesamt bei 23,5 % bzw. bei 13 % in dem ausschließlich nichtkardiochirurgischen Kollektiv. Ergebnisse aus der Literatur legen nahe, dass für eine angemessene externe Validierung eines multivariablen prognostischen Scores etwa 200 „interessierende Ereignisse" beobachtet werden sollten [10]. Unter der Annahme, dass in einigen der beteiligten Zentren keine Kardiochirurgie vertreten ist, rechnen wir konservativ mit einer Inzidenz von 13 %, was zu einer notwendigen Patientenzahl von mindestens $n = 1550$ Patienten führt. Mit dieser Stichprobengröße könnte man die AUC („area under the curve") des PROPDESC-Scores mit einer Genauigkeit von ± 0,025 auf der Grundlage eines 95 %-Konfidenzintervalls schätzen. Um Ausfälle aufgrund fehlender POD-Tests zu kompensieren, die bis zu 35 % der Studienstichprobe ausmachen können, planen wir, $n = 2400$ Patienten einzubeziehen.

Ethik

Die Studie wurde von der Ethikkommission der Medizinischen Fakultät des Universitätsklinikums Bonn am 04.05.2022 positiv bewertet (lfd. Nr.: 136/22). Das Universitätsklinikum Bonn übernimmt für jedes teilnehmende Zentrum das Einholen des lokalen Ethikvotums. Die Studie ist im Deutschen Register Klinische Studien unter der Nummer DRKS00028712 registriert.

Aus Qualitätsgründen werden in regelmäßigen Abständen Plausibilitätskontrollen der eingegebenen Daten (Database-Monitoring) durchgeführt. Dieser strukturierte Prozess ist bis zum Ende des Projekts geplant. Bei häufigen Unstimmigkeiten wird eine Vor-Ort-Kontrolle erwogen, um korrekte und valide Daten zu gewährleisten.

Meilensteine

Seit Studienstart im November 2022 konnten 13 Kliniken in ganz Deutschland bis November 2023 bereits 1396 Patienten einschließen. Ende März 2025 soll die geplante Zahl von 2400 Patienten erreicht und die Studie beendet werden. Direkt im Anschluss werden die Daten ausgewertet und veröffentlicht.

Studiengruppe/Expertise

- *Studienleiterin:* Prof. Dr. med. Maria Wittmann
- *stellvertretender Studienleiter:* Dr. med. Jan Menzenbach
- *Studienkoordination:* Vera Guttenthaler und Andrea Kunsorg, Klinik für Anästhesiologie und Operative Intensivmedizin, Universitätsklinikum Bonn
- *Statistiker:* Prof. Dr. Andreas Mayr, Institut für medizinische Biometrie, Informatik und Epidemiologie, Universitätsklinikum Bonn
- *Teilnehmende Zentren:* Uniklinik RWTH Aachen, Cura Krankenhaus Bad Honnef, Charité Berlin, Johanniter Krankenhaus Bonn, Universitätsklinikum Bonn, Klinikum Dortmund, Cellitinnen Krankenhaus Köln, RKH Orthopädische Kliniken Markgröningen, Kreiskrankenhaus Mechernich, LMU München, TU München, Klinikum Barmherzige Brüder Straubing, Universitätsklinikum Würzburg (vollständige Adressen siehe Zusatzmaterial in der Online-Version des Artikels)

Das Studienteam der Klinik für Anästhesiologie am Universitätsklinikum Bonn ist neben der Durchführung von eigenen Stu-

dien wie der Vorgängerstudie PROPDESC auch seit vielen Jahren als renommiertes Studienzentrum im nationalen und internationalen Bereich tätig. Ab Januar 2024 wird es die Funktion des Partnerinstituts des DGAI(Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin)-Studienzentrums übernehmen.

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Förderung. Die Studie wird durch die Deutsche Gesellschaft für Anästhesiologie und Intensivmedizin (DGAI) gefördert.

Einhaltung ethischer Richtlinien

Interessenkonflikt. V. Guttenthaler, A. Kunsorg, A. Mayr, T. Hering, J. Menzenbach und M. Wittmann geben an, dass kein Interessenkonflikt besteht.

Für diesen Beitrag wurden von den Autor/-innen keine Studien an Menschen oder Tieren durchgeführt. Für die aufgeführten Studien gelten die jeweils dort angegebenen ethischen Richtlinien.

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Hinweis des Verlags. Der Verlag bleibt in Hinblick auf geografische Zuordnungen und Gebietsbezeichnungen in veröffentlichten Karten und Institutsadressen neutral.

Buchbesprechung

Dr. Mark Weinert

Der 1-Minuten-Arzt:Einfach. Besser. Kommunizieren.

Das Praxisbuch für Menschen im Gesundheitswesen

Why Not Publishing 2023, 292 S., (ISBN: 978-3347878167), 49,90 EUR

Der 1-Minuten-Arzt: Sicher und besser kommunizieren, für weniger Sand und mehr Öl im Getriebe.

Dieses Buch vermittelt auf erfrischend umgangssprachliche Weise, worauf es bei der Kommunikation in der Medizin ankommt – dass es nun mal um mehr geht als um das einfach gesprochene Wort. Warum ist es wichtig, zwischen Empathie, Mitgefühl und Mitleid zu unterscheiden? Inwiefern spielen Emotionen eine Rolle und kann man Kommunikation wirklich lernen? Was ist eine „Closed-Loop-Kommunikation", wie gebe ich am besten ein Feedback und auf welche Art und Weise kann es mir gelingen, schlagfertig zu sein, obgleich es mich in einer Diskussion kurzzeitig innerlich zu zerreißen droht? Durch praktische Beispiele sehen sich Ärztinnen und Ärzte mit diesem Buch schnell in Situationen versetzt, die ihnen aus dem Alltag bekannt vorkommen. Hierbei werden alle wesentlichen Themen berücksichtigt und alle wesentlichen Fragen rund um das Thema Kommunikation in der Medizin beantwortet.

Das Buch behandelt unter anderem die Kommunikation im Notfallmanagement, die kommunikativen Aspekte in der Arzt-Patienten-Beziehung, beinhaltet Tipps und Tricks für die Führung von Mitarbeitenden, Gespräche mit Angehörigen, adressiert die Kommunikation mit den Medien und Jurist:innen und so vieles mehr, was viele sich wohl bereits im Medizinstudium gewünscht hätten.

4. Discussion with references

4.1 Prediction of postoperative delirium

As POD is a common phenomenon, especially in older patients after cardiac surgery, many studies, reviews, and meta-analysis have tried to associate perioperative circumstances with its occurrence and estimate the possibilities of delirium prediction [Chen et al., 2021; Lindroth et al., 2018; Inouye et al., 2014; Grover, and Kate, 2012; Hshieh et al., 2015; Raats et al., 2015; Zhang et al., 2020; Scholz et al., 2016; Hoogma et al., 2023; Mevorach et al., 2023].

Patients that developed POD might suffer prolonged hospital stays with increased mortality and morbidity, as well as cognitive and functional decline resulting in care dependency with a huge impact on costs for health care systems [Grover, and Kate, 2012]. Therefore - especially in older patients - early detection of patients at risk and implementation of protective measures to prevent its manifestation is crucial for a better patient outcome. Already known onset factors could facilitate POD prediction in some patient groups. Therefore, if effective screening tools are implemented early enough in the course of a planned hospital admission, in-time administration of protective perioperative measures could improve the postoperative outcome of vulnerable patients.

The PROPDESC score focuses on the easy and early detection of patients at risk with good prediction accuracy (AUC 0.746). The accuracy did not reach the comparably high predictive accuracy in the model developed by Kim et al. (AUC = 0.94), [Kim et al., 2016]. However, Kim conducted enrolment in his Delphi trial partly after POD onset and involved data not available prior to surgery for development of his prediction model [Kim et al., 2016]. Further models provided a comparable AUC to PROPDESC score, but relied on information of extensive cognitive testing not applicable as preoperative routine [Lindroth et al., 2018].

The PROPDESC score that has been developed and already been validated internally on the PROPDESC patient sample is momentarily under external validation in the PROPDESC-Val study (PRe-Operative Prediction of postoperative DElirium by appropriate Screening-Validation study) in order to prove the generalizability of the score and to inspire the start of a standardized preoperative screening of POD risk in German hospitals.

To validate the score, 13 German hospitals with different care levels have included more than 2400 patients in the last two years. Feedback of the hospitals should provide insight in the practical feasibility of the PROPDESC score and reveal areas of possibly necessary adjustments to integrate this prediction tool into clinical routine.

4.2 Measures to prevent postoperative delirium

Multifactorial pathogenesis of POD provides the opportunity to apply various measures for prevention. The results of the multi-centre study PROPDESC-Val are expected to serve as a basis for further projects on delirium management with interventional study approaches like Snoezelen aiming at the implementation of effective preventive measures after identifying patients at risk. Snoezelen seems to be an effective tool to reduce the incidence of POD. In the prospective, randomized, controlled, non-pharmacological FEEL WELL study, cardiac surgery patients in the intervention group had a reduction of the delirium incidence by 54.4 % which supports the hypothesis of the trial that the multisensory stimulation on postoperative day 1-3 may reduce the incidence of POD in this critically ill patient group. It adds to other preventive measures like the use of music or bright light therapy or the training of healthcare professionals on delirium awareness [Inouye et al., 2014; Inouye et al., 1999; Marcantonio et al., 2001; Hshieh et al., 2015; Chen et al., 2011; Caplan, and Harper, 2007; McCaffrey, and Locsin, 2004; Lundström et al., 2005; McCaffrey, 2009; Ono et al., 2011]. Although preoperative evaluation scores were worse, the length of ICU stay was shorter in our intervention group. One component of this multifactorial situation may have been the positive effect of Snoezelen treatment on the recovery and well-being of patients. The median duration of mechanical ventilation after surgery in the ICU was 0 hours in the intervention group and 3 hours in the control group. Prolonged mechanical ventilation might be associated with prolonged intensive care admission and delirium [Chen et al., 2021; Trudzinski et al., 2022; Burkhart et al., 2010]. This may be one of the reasons for prolonged ICU-stay and higher delirium rates in the control group. The length of stay in hospital after surgery was similar in both study groups. As many factors could influence the length of hospital stay in older patients undergoing cardiac surgery, [Engelman et al., 2019; Waite et al., 2017], this outcome may not be altered significantly by correction of a single parameter.

As shown in literature, non-pharmacological interventions, aimed at accelerating the recovery and well-being of patients, can shorten the duration of hospitalization which may also shorten the length of ICU stay as well [Chen et al., 2017; Chen et al., 2011; Lundström et al., 2005]. In the mHELP (Modified Hospital Elder Life Program) study Chen et al found that orienting communication, oral and nutritional assistance, and early mobilization reduced delirium incidence by 56% and LOS in hospital LOS by 2 days [Chen et al., 2017].

Nevertheless, although Snoezelen does not shorten the length of hospitalization, it reduces the length of stay in the ICU. Since prolonged length of stay in the ICU is associated with serious complications like resistant infections, it is important to shorten this period (41).

Furthermore, pain scores were significantly lower in the intervention group on day four and five ($p=0.022$; $p<0.001$, respectively). Although there were many missing values in the pain assessment on the fifth postoperative day, distribution of these missing values was similar between the intervention and the control group. Many studies have shown that Snoezelen treatment reduces agitation and anxiety in target groups and increases well-being [Pinto et al., 2020; Baker et al., 2001; Sánchez et al., 2013; Sánchez et al., 2016; Milev et al., 2008; Van Weert et al., 2005; Strøm et al., 2016; Chung et al., 2002]. The reduction of the pain scores after 3 times of Snoezelen could lead to the conclusion, that the intervention could reduce anxiety and improve the well-being of the patient which could lead to a decrease of the pain scores.

4.3. Aspects of effective screening tools

Preoperative alcohol consumption is a risk factor for POD [Wu et al., 2023; Karageorgos et al., 2023]. Detecting patients at risk early provides the treating physician with the opportunity to initiate preventive measures as preoperative alcohol reduction could lead to a better postoperative outcome by improving several organic dysfunctions and in consequence reducing postoperative morbidity [Tønnesen, 2003]. Discontinuation of alcohol consumption four to eight weeks prior to any surgical procedure could potentially decrease the incidence of postoperative complications [Egholm et al., 2018].

A challenge could be the accurate detection of health-relevant alcohol consumption.

In a sub-analysis within the PROPDESC study the AUDIT-C proved his ability to assess preoperative alcohol consumption among older surgical patients. An early detection of

patients with AUD (Alcohol use disorder) is very important in a clinical setting as this provides the opportunity to encourage preoperative alcohol reduction.

Additionally, detection of risky alcohol intake needs to be accurate taking into consideration that reliable testimony about alcohol consumption could depend on the setting in which the interview is posed. A person to person interview regarding a sensitive topic like alcohol consumption can lead to evasive answers. Kip et al. found that the prevalence rate of AUD determined by anesthesiologists was 6.9 % compared to 18.1 % if AUD was assessed using a computerized version of the AUDIT [Kip et al., 2008].

Inaccurate assessment of alcohol consumption may lead to the selective identification of individuals with severe alcohol dependency while overlooking patients who drink above recommended limits [Shourie et al., 2007]. The results of our study show, that patient´s responses can differ considerably depending on how alcohol use is addressed during the routine pre-clinic visit prior to hospital admission. Of the patients that negated the SSQ about daily alcohol consumption and answered positive on the AUDIT-C questionnaire, 25.1 % reported moderate (11.2 %) to high (13.9 %) alcohol consumption.

An important aspect for acceptance of a screening tool for alcohol consumption in the daily clinical setting is suitability for self-completion. The AUDIT-C has proven its sensitivity and specificity in various different settings and appears to be as good as if not better than the AUDIT [Berks, and McCormick, 2008] and national guidelines recommend the AUDIT questionnaire as a screening tool of at-risk alcohol consumption, harmful use or alcohol dependence and suggest the use of the AUDIT-C [Kiefer et al., 2022; Recommendations | Alcohol-use disorders: prevention | Guidance | NICE, 2010].

Ease of completion is also the aim of PROPDESC score. It was generated as a universal pragmatic risk score based on preoperative data from patients of various surgical disciplines. Predicting the patient´s risk of delirium offers the opportunity to identify high-risk patients preoperatively and to initiate delirium-preventive measures. The PROPDESC score focuses on perioperative predisposing and precipitating factors in order to establish an easy applicable screening tool. Further studies might be useful to evaluate, if the use of the AUDIT-C together with the PROPDESC score could improve the accuracy of the score as some other models have already included alcohol consumption in their risk assessment

[van Meenen et al., 2014]. Since laboratory values are usually determined shortly before surgery, it only makes sense to include these predictive values in a risk prediction model if there is enough time to take corrective measures before the operation.

4.4 Conclusion

The combination of preoperative identification of patients at risk for POD and interventions to reduce the occurrence of POD has been in the focus of research for many years, with an emphasis on older surgical patients. As the entity POD is so diverse, a synthesis of prediction through early identification and prevention via perioperative optimization is needed to reduce the incidence and severity of POD, which remains a major concern, particularly for older patients with high risk surgeries like cardiac surgery. One promising screening tool that encompasses various risk factors of POD is the PROPDESC score, developed for a time-saving assessment using almost completely preoperative routine values and only two additional questions regarding preexisting cognitive deficits. This score could be complemented by the preoperative evaluation of alcohol consumption via the AUDIT-C. Accurate screening for a patient´s alcohol consumption is important for identifying patients at risk for AWS and POD and a timely reduction of alcohol consumption before an upcoming surgery could support a better outcome. Routine laboratory values that indicate anemia or dehydration may additionally complement the PROPDESC score as a screening tool to identify early indicators for pathophysiological states which can predispose patients for POD. To prevent the occurrence of POD in vulnerable patients we identified snoezelen as a possible postoperative routine that could reduce the incidence of POD significantly. Therefore, in order to protect vulnerable patients from POD, accurate prediction tools and suitable prevention measures have to be implemented in the complete perioperative routine since only a multi-disciplinary intervention could counteract the diverse entity POD.

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6. Statement

The work was carried out at the University Hospital Bonn under the supervision of Prof. Dr. Maria Wittmann. In the PROPDESC study Vera Guttenthaler participated in design, protocol writing, methodology, and application for study funding in collaboration with Jan Menzenbach, Head of the Pre-Admission Clinic and Maria Wittmann, Head of the Clinical Study Team at the Clinic of Anesthesia, University Hospital Bonn. Vera Guttenthaler applied for the ethics vote for the PROPDESC study and participated in the setup of the data collection tools (eCRF, RedCap), and in the selection and implementation of the used questionnaires, especially the AUDIT-C, in the study. The data for the PROPDESC study was generated in collaboration with Jan Menzenbach, Andrea Kunsorg, scientist at the University Hospital Bonn, Johanna Feggeler, resident at the University Hospital Bonn, and the PROPDESC study team. Vera Guttenthaler participated in the data analysis and Andreas Mayr, statistician at the Institute for Medical Biometrics, Informatics, and Epidemiology (IMBIE), Andrea Kunsorg, and Christian Staerk, statistician at the Institute for Medical Biometrics, Informatics, and Epidemiology (IMBIE) completed the detailed analysis of the patient sample. Angelo Ricchiutto, Clinical data manager, Institute for Medical Biometrics, Informatics, and Epidemiology (IMBIE) supported the eCRF, Mark Coburn, Head of the Clinic of Anesthesia and Intensive Care Medicine of the University Hospital Bonn and Tobias Hilbert, managing senior physician at the Clinic of Anesthesia and Intensive Care Medicine of the University Hospital Bonn supported the study conduction. Jan Menzenbach and Maria Wittmann supervised the study. The publication “Predictiveness of preoperative laboratory values for postoperative delirium” was written in collaboration with Jacqueline Fidorra, back then medical student, with the data of the PROPDESC study and Vera Guttenthaler contributed to this publication providing additionally support for background information, discussion, and interpretation of the results. As this was a subgroup analysis of the PROPDESC study, all her contributions for the PROPDESC study apply to this publication as well. Jacqueline Fidorra evaluated the data. The manuscript was prepared by Vera Guttenthaler, Jacqueline Fidorra, and Jan Menzenbach. Maria Wittmann provided guidance throughout the design and conduction of the study and reviewed the manuscript. For the publication “Preoperative evaluation of alcohol consumption in older patients” the data of the PROPDESC study was used. First data analysis, writing of the manuscript, data interpretation, and discussion of the results

was done by Vera Guttenthaler. Data analysis was supported by Andrea Kunsorg. Vera Guttenthaler wrote the study protocol for the PROPDESC-Val study, applied for the Ethics vote of all participating study sites, participated in the set-up of the data collection tool (eCRF) in collaboration with Maria Wittmann and David Rowlands. In the PROPDESC-Val study the data was generated in collaboration with the study teams of the participating study sites, especially Theresa Hering, resident at the Kreiskrankenhaus Mechernich, Tugce Dinc-Dogan, physician at the University Hospital Bonn, Gregor Massoth, senior physician at the University Hospital Bonn, and Thomas Saller, managing senior physician at the Clinic of Anesthesia at the University Hospital of the LMU, Munich. The statistical evaluation of the PROPDESC-Val study has not started yet. Data query management and interim analysis of the data was carried out by Vera Guttenthaler. For the FEEL WELL study Vera Guttenthaler wrote the synopsis and applied for the ethics vote. Application for funding via the Deutsche Herzstifung was done by Vera Guttenthaler in collaboration with Maria Wittmann and Tugce Dinc-Dogan. Procurement of necessary equipment and support with documentation, randomization, and patient visit plans was done by Vera Guttenthaler. Vera Guttenthaler provided additional patient data to complete patient characterization. Tugce Dinc-Dogan, Alexa Zimmermann, medical student at the University Hospital Bonn, Merve Özlem Dinc, resident at the Department of Anesthesia and Intensive Care, Istanbul University, Istanbul Medical Faculty, and Niko Knülle, medical student at the University Hospital Bonn, performed the interventions and tests. Jens-Christian Schewe, senior physician at the University Hospital Bonn, helped implementing the study in the intensive care unit. Tugce Dinc-Dogan and Andrea Kunsorg performed the statistical analysis of the data and wrote the statistical part of the manuscript. I supported the data analysation, the data interpretation, and wrote the manuscript together with Tugce Dinc-Dogan.

I confirm that I have written this thesis independently and have not used any sources or aids other than those specified by me.