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ORIGINAL RESEARCH

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Predictiveness of preoperative laboratory values for postoperative delirium

Vera Guttenthaler[1] | Jacqueline Fidorra[1,2] | Maria Wittmann[1] | Jan Menzenbach[1]

[1]Clinic of Anaesthesia and Intensive Care Medicine, University Bonn, Bonn, Germany

[2]Asklepios Clinic North Heidberg, Clinic for Internal Medicine Department I, Hamburg, Germany

Correspondence
Jan Menzenbach, Clinic of Anaesthesia and Intensive Care Medicine, University Hospital Bonn, Venusberg-Campus 1, 53127 Bonn, Germany.
Email: Jan.Menzenbach@ukbonn.de

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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.

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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

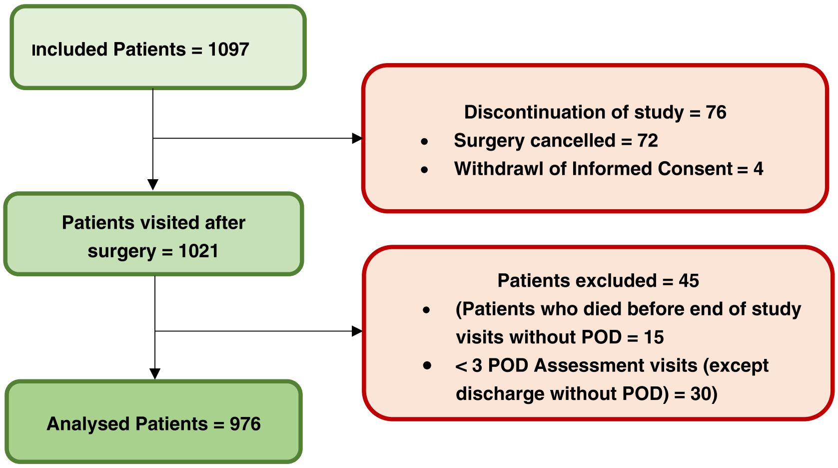

FIGURE 1 Patients participating in the PROPDESC study (modified after Menzenbach et al. 2022).[24] POD, postoperative delirium.

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.

ORCID

Vera Guttenthaler http://orcid.org/0000-0001-6466-9780
Jacqueline Fidorra http://orcid.org/0009-0004-4978-5555
Maria Wittmann http://orcid.org/0000-0003-4786-7712
Jan Menzenbach http://orcid.org/0000-0002-1525-6450

REFERENCES

1. Drews T, Franck M, Radtke FM, et al. Postoperative delirium is an independent risk factor for posttraumatic stress disorder in the elderly patient: a prospective observational study. *Eur J Anaesthesiol*. 2015;32(3):147-151.
2. Inouye SK, Marcantonio ER, Kosar CM, et al. The short-term and long-term relationship between delirium and cognitive trajectory in older surgical patients. *Alzheimer's Dementia*. 2016;12(7):766-775.
3. Marcantonio ER. Delirium in hospitalized older adults. *N Engl J Med*. 2017;377(15):1456-1466.
4. ICD-11 for mortality and morbidity statistics [Internet]. 2023. https://icd.who.int/browse11/l-m/en#/http%3a%2f%2fid.who.int%2ficd%2fentity%2f897917531
5. Jin Z, Hu J, Ma D. Postoperative delirium: perioperative assessment, risk reduction, and management. *Br J Anaesth*. 2020;125(4):492-504.
6. Marcantonio ER. Postoperative delirium. *JAMA*. 2012;308(1):73-81.
7. Aldecoa C, Bettelli G, Bilotta F, et al. European Society of Anaesthesiology evidence-based and consensus-based guideline on postoperative delirium. *Eur J Anaesthesiol*. 2017;34(4):192-214.
8. Liu Y, Zhang Q, Zhao Y, et al. Delirium screening tools. *Medicine*. 2020;99(35):e21595.
9. Prieto GA, Tong L, Smith ED, Cotman CW. TNFα and IL-1β but not IL-18 suppresses hippocampal long-term potentiation directly at the synapse. *Neurochem Res*. 2019;44(1):49-60.
10. Dandona P, Chaudhuri A, Mohanty P, Ghanim H. Anti-inflammatory effects of insulin. *Curr Opin Clin Nutr Metab Care*. 2007;10(4):511-517.
11. Hyun E, Ramachandran R, Hollenberg MD, Vergnolle N. Mechanisms behind the anti-inflammatory actions of insulin. *Critical Reviews™ Immunol*. 2011;31(4):307-340.
12. Raats JW, van Eijsden WA, Crolla RMPH, Steyerberg EW, van der Laan L. Risk factors and outcomes for postoperative delirium after major surgery in elderly patients. *PLoS One*. 2015;10(8):e0136071.
13. Galanakis P, Bickel H, Gradinger R, Von Gumppenberg S, Förstl H. Acute confusional state in the elderly following hip surgery: incidence, risk factors and complications. *Int J Geriatr Psychiatry*. 2001;16(4):349-355.
14. Zhang HJ, Ma XH, Ye JB, Liu CZ, Zhou ZY. Systematic review and meta-analysis of risk factor for postoperative delirium following spinal surgery. *J Orthop Surg Res*. 2020;15:509.
15. Scholz AFM, Oldroyd C, McCarthy K, Quinn TJ, Hewitt J. Systematic review and meta-analysis of risk factors for postoperative delirium among older patients undergoing gastrointestinal surgery. *Br J Surg*. 2016;103(2):e21-e28.
16. Smulter N, Lingehall HC, Gustafson Y, Olofsson B, Engström KG. Delirium after cardiac surgery: incidence and risk factors. *Interact Cardiovasc Thorac Surg*. 2013;17(5):790-796.
17. Hoogma DF, Milisen K, Rex S, Al Tmimi L. Postoperative delirium: identifying the patient at risk and altering the course: a narrative review. *Eur J Anaesthesiol Intensive Care*. 2023;2(3):e0022.
18. Mevorach L, Forookhi A, Farcomeni A, Romagnoli S, Bilotta F. Perioperative risk factors associated with increased incidence of postoperative delirium: systematic review, meta-analysis, and grading of recommendations assessment, development, and evaluation system report of clinical literature. *Br J Anaesth*. 2023;130(2):e254-e262.
19. Fong TG, Bogardus ST, Daftary A, et al. Cerebral perfusion changes in older delirious patients using 99mTc HMPAO SPECT. *J Gerontol A Biol Sci Med Sci*. 2006;61(12):1294-1299.
20. Yokota H, Ogawa S, Kurokawa A, Yamamoto Y. Regional cerebral blood flow in delirium patients. *Psychiatry Clin Neurosci*. 2003;57(3):337-339.
21. Athilingam P, Moynihan J, Chen L, D'Aoust R, Groer M, Kip K. Elevated levels of interleukin 6 and C-reactive protein associated with cognitive impairment in heart failure. *Congestive Heart Failure*. 2013;19(2):92-98.
22. de la Torre JC. Cardiovascular risk factors promote brain hypoperfusion leading to cognitive decline and dementia. *Cardiovasc Psychiatry Neurol*. 2012;2012:1-15.
23. Menzenbach J, Guttenthaler V, Kirfel A, et al. Estimating patients' risk for postoperative delirium from preoperative routine data: trial design of the PRe-Operative prediction of postoperative DElirium by appropriate SCreening (PROPDESC) study: a monocentre prospective observational trial. *Contemp Clin Trials Commun [Internet]*. 2019;17:100501. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6926123
24. Menzenbach J, Kirfel A, Guttenthaler V, et al. 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. *J Clin Anesth*. 2022;78:110684.
25. Donati A, Ruzzi M, Adrario E, et al. A new and feasible model for predicting operative risk. *Br J Anaesth*. 2004;93(3):393-399.
26. Deutsche Diabetes Gesellschaft. Positionspapier der Deutschen Diabetes Gesellschaft zur Therapie des Diabetes mellitus im Krankenhaus. 2016;103.
27. Bundesärztekammer auf Empfehlung ihres Wissenschaftlichen Beiratsed. *Querschnitts-Leitlinien zur Therapie mit Blutkomponenten und Plasmaderivaten: Gesamtnovelle 2020 [Internet]*. Deutscher Ärzteverlag; 2021. doi:10.47420/9783769137309
28. World Health Organization. Haemoglobin concentrations for the diagnosis of anaemia and assessment of severity; 2011.
29. Rivas-Ruiz R, Moreno-Palacios J, Talavera JO. [Clinical research XVI. Differences between medians with the Mann-Whitney U test]. *Rev Med Inst Mex Seguro Soc*. 2013;51(4):414-419.
30. Böhmer A, Defosse J, Geldner G, et al. The updated ASA classification; 2022.
31. Saklad M. Grading of patients for surgical procedures. *Anesthesiology*. 1941;2(3):281-284.
32. Commitee on Standards and Practice Parameters, Apfelbaum JL, Connis RT, et al. Practice advisory for preanesthesia evaluation. *Anesthesiology*. 2012;116(3):522-538.
33. Pasternak RL. Preanesthesia evaluation of the surgical patient. *ASA Refresher Courses Anesthesiol*. 1996;24:205-219.
34. Kim MY, Park UJ, Kim HT, Cho WH. DELirium prediction based on hospital information (Delphi) in general surgery patients. *Medicine*. 2016;95(12):3072. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4998372
35. Ha A, Krasnow RE, Mossanen M, et al. A contemporary population-based analysis of the incidence, cost, and outcomes of postoperative delirium following major urologic cancer surgeries. *Urol Oncol: Seminars Original Investig*. 2018;36(7):341.e15-341.e22.
36. Rudolph JL, Jones RN, Levkoff SE, et al. Derivation and validation of a preoperative prediction rule for delirium after cardiac surgery. *Circulation*. 2009;119(2):229-236.
37. Daiello LA, Racine AM, Yun Gou R, et al. Postoperative delirium and postoperative cognitive dysfunction. *Anesthesiology*. 2019;131(3):477-491.
38. Radtke FM, Franck M, MacGuill M, et al. Duration of fluid fasting and choice of analgesic are modifiable factors for early postoperative delirium. *Eur J Anaesthesiol*. 2010;27(5):411-416.

39. Ormseth CH, LaHue SC, Oldham MA, Josephson SA, Whitaker E, Douglas VC. Predisposing and precipitating factors associated with delirium. *JAMA Network Open*. 2023;6(1):e2249950.
40. Kunz JV, Spies CD, Bichmann A, Sieg M, Mueller A. Postoperative anaemia might be a risk factor for postoperative delirium and prolonged hospital stay: a secondary analysis of a prospective cohort study. *PLoS One*. 2020;15(2):e0229325.
41. Chaiwat O, Chanidnuan M, Pancharoen W, et al. Postoperative delirium in critically ill surgical patients: incidence, risk factors, and predictive scores. *BMC Anesthesiol*. 2019;19:39.
42. Park SA, Tomimaru Y, Shibata A, Miyagawa S, Noguchi K, Dono K. Incidence and risk factors for postoperative delirium in patients after hepatectomy. *World J Surg*. 2017;41(11):2847-2853.
43. Kotfis K, Szylińska A, Listewnik M, Brykczyński M, Ely EW, Rotter I. Diabetes and elevated preoperative HbA1c level as risk factors for postoperative delirium after cardiac surgery: an observational cohort study. *Neuropsychiatr Dis Treat*. 2019;15:511-521.
44. Ansaloni L, Catena F, Chattat R, et al. Risk factors and incidence of postoperative delirium in elderly patients after elective and emergency surgery. *Br J Surg*. 2010;97(2):273-280.
45. Dronge AS, Perkal MF, Kancir S, Concato J, Aslan M, Rosenthal RA. Long-term glycemic control and postoperative infectious complications. *Archiv Surg (Chicago, Ill.: 1960)*. 2006;141(4):375-380; Discussion 380.
46. Frisch A, Chandra P, Smiley D, et al. Prevalence and clinical outcome of hyperglycemia in the perioperative period in noncardiac surgery. *Diabetes Care*. 2010;33(8):1783-1788.
47. Halkos ME, Lattouf OM, Puskas JD, et al. Elevated preoperative hemoglobin A1c level is associated with reduced long-term survival after coronary artery bypass surgery. *Ann Thorac Surg*. 2008;86(5):1431-1437.
48. Walid MS, Newman BF, Yelverton JC, Nutter JP, Ajjan M, Robinson JS. Prevalence of previously unknown elevation of glycosylated hemoglobin in spine surgery patients and impact on length of stay and total cost. *J Hospital Med*. 2010;5(1):E10-E14.
49. Yang S, Gu C, Mandeville ET, et al. Anesthesia and surgery impair blood–brain barrier and cognitive function in mice. *Front Immunol*. 2017;8:902.
50. Terrando N, Eriksson LI, Kyu Ryu J, et al. Resolving postoperative neuroinflammation and cognitive decline. *Ann Neurol*. 2011;70(6):986-995.
51. Toft K, Tontsch J, Abdelhamid S, Steiner L, Siegemund M, Hollinger A. Serum biomarkers of delirium in the elderly: a narrative review. *Ann Intensive Care*. 2019;9(1):76.
52. Bakker RC, Osse RJ, Tulen JHM, Kappetein AP, Bogers AJJC. Preoperative and operative predictors of delirium after cardiac surgery in elderly patients. *Eur J Cardiothorac Surg*. 2012;41(3):544-549.
53. Hatano Y, Narumoto J, Shibata K, et al. White-matter hyperintensities predict delirium after cardiac surgery. *Am J Geriatr Psychiatry*. 2013;21(10):938-945.
54. Miyazaki S, Yoshitani K, Miura N, et al. Risk factors of stroke and delirium after off-pump coronary artery bypass surgery. *Interact Cardiovasc Thorac Surg*. 2011;12(3):379-383.
55. Tan MC, Felde A, Kuskowski M, et al. Incidence and predictors of post-cardiotomy delirium. *Am J Geriatr Psychiatry*. 2008;16(7):575-583.
56. Lee SH, Lim SW. Risk factors for postoperative delirium after colorectal surgery: a systematic review and meta-analysis. *Int J Colorectal Dis*. 2020;35(3):433-444.
57. Parente D, Luís C, Veiga D, Silva H, Abelha F. Congestive heart failure as a determinant of postoperative delirium. *Rev Port Cardiol*. 2013;32(9):665-671.
58. Bucerius J, Gummert JF, Borger MA, et al. Predictors of delirium after cardiac surgery delirium: effect of beating-heart (off-pump) surgery. *J Thorac Cardiovasc Surg*. 2004;127(1):57-64.
59. Uthamalingam S, Gurm GS, Daley M, Flynn J, Capodilupo R. Usefulness of acute delirium as a predictor of adverse outcomes in patients >65 years of age with acute decompensated heart failure. *Am J Cardiol*. 2011;108(3):402-408.
60. Robinson TN, Raeburn CD, Tran ZV, Angles EM, Brenner LA, Moss M. Postoperative delirium in the elderly: risk factors and outcomes. *Ann Surg*. 2009;249(1):173-178.

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