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ARTIGO DE ORIGINAL

Delirium Pós-Operatório Após Cirurgia Neoplásica

Postoperative Delirium After Cancer Surgery

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RESUMO

Introdução: O *delirium* pós-operatório (DPO) é um dos eventos adversos mais comuns relacionados com a cirurgia. O objetivo do estudo foi avaliar a DPO e sua incidência, características e impacto na recuperação após a cirurgia oncológica.

Material e Métodos: Após aprovação pela Comissão de Ética do Centro Hospitalar São João, realizou-se um estudo observacional prospetivo com 148 doentes submetidos a cirurgia neoplásica eletiva. O resultado primário foi o DPO e o secundário a qualidade de recuperação. Diagnosticou-se DPO com o *Nursing Delirium Screening Scale* e a qualidade de recuperação com o Postoperative Quality of Recovery Scale e o questionário *Quality of Recovery 15* (QoR-15).

Resultados: POD ocorreu em 16% dos doentes. Estes tinham uma classificação ASA-*Physical Status* superior (p = 0,004), foram submetidos mais frequentemente a cirurgia major (p = 0,007), apresentavam mais frequentemente insuficiência cardíaca (p < 0.001), diabetes *mellitus* insulinodependente (p = 0,006), pontuações superiores no *Revised Cardiac Risk Index* (p = 0,013), tiveram mais problemas no autocuidado (p = 0,001) e nas atividades de vida diária (p = 0,02) do EQ-5D. No PQRS, tiveram uma menor recuperação completa no primeiro dia pós-operatório para o domínio fisiológico (p = 0,007) e domínio funcional (p = 0,047) e tiveram menores pontuações de QoR-15 (p = 0,001). Tiveram cirurgias mais longas (p = 0,002) e maior tempo de internamento na UPA (p = 0,004) e hospital (p = 0,002).

Discussão e Conclusão: DPO foi frequente após cirurgia neoplásica. Eram doentes mais velhos, tinham mais comorbilidades, foram mais frequentemente submetidos a cirurgia *major*, tinham pior qualidade de vida antes da intervenção e tiveram uma recuperação pior e menos completa.

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ABSTRACT

Introduction: Postoperative delirium (POD) is one of the most common adverse events related to surgery. This study aimed to evaluate POD and its incidence, characteristics and impact on the recovery after cancer surgery.

Materials and Methods: After approval by Institutional Review Board of the Centro Hospitalar São João, a prospective observational study was performed enrolling 148 adult participants submitted to elective neoplastic surgery. Primary outcome was postoperative delirium (POD) and secondary outcome was quality of recovery. POD was evaluated with Nursing Delirium Screening Scale and quality of recovery was assessed with Postoperative Quality of Recovery Scale (PQRS) and 15-item Quality of Recovery (QoR-15).

Results: POD developed in 16% of patients. POD patients were older (p < 0.001), had higher ASA physical status (p = 0.004), were more often submitted to major surgery (p = 0.007), had more frequently heart failure (p < 0.001), insulin-dependent diabetes mellitus (p = 0.006), a higher Revised Cardiac Risk Index (p = 0.013); they had more problems in self-care (p = 0.001) and daily life activities (p = 0.02) on EQ-5D. In PQRS, POD patients had a lower rate of complete recovery at postoperative day one for physiological domain (p = 0.007) and functional domain (p = 0.047) and had a lower median total QoR-15 score (p = 0.001). POD patients had longer surgery duration (p = 0.002), longer length of stay at PACU (p = 0.004) and hospital (p = 0.002).

Discussion and Conclusion: POD was frequent after neoplastic surgery. Patients with POD were older, had more comorbidities were more frequently submitted to major surgery, had a worse quality of life before intervention and had a worse and less complete recovery.

INTRODUCTION

A recent analysis from the European Cancer Registry database showed an increase in cancer incidence.[1] As life expectancy increases, diseases like cancer emerge as a top

cause of morbidity and mortality.[1-3]

According to the PORDATA Contemporary Portugal Database, in Portugal, in 2016 cancer was the second cause of death with a death rate of around 24.6% just behind cardiovascular diseases with a rate of 29.5%.[4]

Surgery is cancer's hallmark treatment. However, despite surgery's progress, with a longer life expectancy, comes more diseases, disability, functional decline and frailty.[3,5]

Postoperative delirium[6] is one of the most common adverse events related to surgery, with recent researches identifying rates ranging from 5% to 50%[7,8] Particularly after cancer surgery there are reports of a 50% incidence.[9]

Delirium, also referred as an 'acute confusional state', is a transient, global cognitive disorder.

The diagnosis of delirium currently relies on the diagnostic criteria of the American Psychiatric Association's fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[10] and from World Health Organization, The International Classification of Mental and Behavioral Disorders (ICD-10). The definition excludes "delirium induced by alcohol and other psychoactive substances"[11] and includes changes in psychomotor behavior, as well disturbance in circadian rhythm.[11,12]

The Nursing Delirium Symptom Checklist (NuDESC) is a delirium screening tool used to evaluate patients in the Post-Anesthesia Care Unit PACU where it had a sensitivity and specificity of 95% and 87%, respectively.[13]

Moreover, based on motor activity, delirium may be classified as hyperactive (agitated, restlessness patients), hypoactive (calm, lethargic patients) or a mixed one.[12,14,15]

POD usually occurs hours to days following surgery, generally after postoperative day one, has a fluctuating course and must be differentiated from emergent delirium.[12,14,15]

There are many poor outcomes associated with POD. Patients are more likely to have higher rates of surgical complications, a longer hospital stay, higher hospital mortality and, in critically ill patients, longer duration of mechanical ventilation and length of stay in the intensive care unit,[16] with greater health costs.[14,17-20]

In the long term, POD is associated with poor outcomes such as post-discharge institutionalization, higher likelihood of death, with studies pointing to a higher risk of adverse events during the subsequent 30 days, 3 months or 6 months.[18,21,22]

In a 2010 meta-analysis, Witlox *et al,*[20] showed that association of POD with those poor outcomes is independent of important confounders, such as age, sex, comorbidities or disease severity. Pisani and colleagues[23] obtained similar results in critical care patients.

Regarding mortality rate, it is important to refer that some studies found insufficient evidence to prove a causal relationship between mortality and POD *per se*,[7] while others assume a different conclusion, linking POD with higher mortality.[19,23,24]

When studying POD, cognitive decline is an important outcome. Many authors have searched for cognitive modifications in patients having POD, with some authors concluding that those patients experienced a significant acceleration of cognitive decline, with the duration of POD having a role in worsening of global cognition.[17,25-28]

Although POD has clearly defined the mechanisms, underlying POD remain poorly understood. Over the last few years, some authors tried to reach the underlying basis of a multifactorial mechanism.[23] Surgical stress and inflammatory response to trauma, an inflammatory chronic state characteristic of older people, depth of anesthesia and its neurotoxicity, or the interference with acetylcholine synthesis, were possible causes investigated.[27,29-31]

Although many doubts regarding POD basis still exists, we can prevent it, knowing its risk factors. Having different risk factors associated with POD, many authors believe that POD results of multiple contributing factors such patient intrinsic factors (older age, cognitive impairment, American Society of Anesthesiologists physical status (ASA-PS), functional dependence, psychological symptoms, reduction of vision or hearing, medications, concomitant diseases, infections) and extrinsic factors like surgery (emergency surgery, major surgery, duration, complications, hypoxia) and anesthesia (type, depth), which would interact with each other.[7,17,18,25,32]

This prospective observational study aimed to evaluate the incidence, characteristics, and impact impact on the recovery after cancer surgery.

MATERIAL AND METHODS

Study drawing and patient selection

During a 4 months period, between June and September 2016, we carried out an observational prospective cohort study, enrolling patients scheduled for elective neoplastic surgery, in the multidisciplinary PACU of Centro Hospitalar São João (CHSJ), a University Hospital and a reference health unit in Porto, Portugal.

Ethical approval for this study was provided by the Institutional Review Board of the CHSJ (Centro Hospitalar São João Ethics Committee, Ethical approval number 198-13), and before surgery written informed consent was obtained from all participating patients.

Eligible participants were adult patients (more than 18 years old) submitted to urologic, plastic, gynaecologic and general elective neoplastic surgery, admitted to the PACU. We excluded patients in case of refusal, inability to speak Portuguese language fluently or give informed consent and patients with cognitive impairment (Mini-mental State Examination (MMSE) < 24).

Study procedures and data collection

Baseline variables such as age, sex, educational level, body weight, height, body mass index (BMI), American Society of Anesthesiologists Physical Status (ASA-PS) and Charlson comorbidity score were registered preoperatively (T0). Moreover, we recorded other clinical features as pre-admission comorbidities (Table 1) and usual medication at T0.

To estimate a patient's cardiac risk, we used the Revised Cardiac Risk Index (RCRI).[33] The surgical procedure's magnitude was classified as major (surgery in which body cavities or major vessels are exposed to ambient temperature, or a surgery requiring a hospital stay of 2 or more days), medium (surgery in which body cavities are exposed to a lesser degree), and minor surgery (superficial surgery).

We applied the Portuguese version[34] of EuroQol five-dimension questionnaire (EQ-5D) preoperatively (T0) and on the first postoperative day (D1).

Results are presenting in a dichotomic way: having problems, not having problems.

Disability and frailty evaluations were performed, using the World Health Organization Disability Assessment Schedule (WHODAS 2.0)[35] and Clinical Frailty Scale (CFS),[36] respectively. Disability was considered for patients having a total WHODAS score ≥ than 25 and frailty if patients had more than 3 points in CFS.

Intraoperatively, documented details included the type and duration of anesthesia, duration of surgery, drugs, and fluids intraoperatively administered. We managed patients according to the department's standards and registered data from the anesthesia-dedicated software (PICIS®).

The primary outcome was screened by the research team using the Portuguese version[37] of NuDESC. Patients were evaluated for POD by the research team at the time of discharge from the PACU to the regular ward. The research team performing the delirium scoring did not intervene in the patients' care or interfere with the routine recovery room protocol. The recovery room physicians and nurses were blinded to the results of the study but were informed for the result if a patient had POD.

The NuDESC assesses five dimensions of cardinal features of delirium: orientation, behavior, communication, perceptions, and psychomotor activity, with each symptom rated on a 3-point scale (0, 1 or 2). We considered delirium positive if patients had a Nu-DESC cumulative score of 2 or higher, out of 10.[37]

Concerning the evaluation of the quality of recovery (QoR), Postoperative Quality of Recovery Scale (PQRS) was used at baseline (T0) and after surgery at minute 15 (T15), 40 (T40) and day 1 (D1). To complete this evaluation, we asked a series of questions, quantifying objectively the quality of patients' recovery in five domains: physiologic (PD), nociceptive (ND),

Table 1. Baseline characteristics in patients with and without POD

CHARACTERISTICS	n	POD (n=23)	NON-POD (n=125)	*p*
Age (years) (IQR)	148	73 (65-78)	63 (53-73)	0.001[b]
Sex				0.615[a]
Male	83	14 (61%)	69 (55%)	
Female	65	9 (39%)	56 (45%)	
ASA physical status				0.004[a]
I/II	97	9 (39%)	88 (70%)	
III/IV	51	14 (61%)	37 (30%)	
Major surgery				0.007[a]
Yes	59	15 (65%)	44 (35%)	
No	89	8 (34%)	81 (65%)	
Coronary disease				0.205[a]
Yes	21	5 (22%)	16 (13%)	
No	127	18 (78%)	109 (87%)	
Heart failure				<0.001[a]
Yes	17	8 (35%)	9 (7%)	
No	131	15 (65%)	116 (93%)	
Insulin-dependent diabetes mellitus				0.006[c]
Yes	8	4 (17%)	4 (3%)	
No	140	19 (83%)	121 (97%)	
Renal insufficiency				0.109[b]
Yes	8	3 (13%)	5 (4%)	
No	140	20 (87%)	120 (96%)	
CVD				0.114[b]
Yes	4	2 (19%)	2 (2%)	
No	144	21 (91%)	123 (98%)	
RCRI				0.013[a]
< 2	123	15 (65%)	108 (86%)	
≥ 2	25	8 (35%)	17 (14%)	
BDZ medication	27	5 (22%)	22 (18%)	0.413[a]
Type of anesthesia				
General	102	19 (82%)	83 (66%)	0.123[a]
Regional	11	1 (4%)	10 (8%)	0.460[c]
Combined	33	3 (13%)	30 (24%)	0.190[c]
Sedation/Analgesia	2	0 (0%)	2 (2%)	0.712[c]
Duration/Length of stay				
BDZ premedication	31	8 (35%)	23 (18%)	0.066[a]
Surgery duration (minutes)	148	160 (111-125)	116 (80-160)	0.002[b]
PACU (minutes) median IQR	148	237 (138-1000)	128 (90-205)	0.004[b]
Hospital (days) median IQR	148	26.5	1	0.002[b]

LEGENDA:
PACU, Post-Anesthesia Care Unit; POD, Postoperative delirium; ASA, American Society of Anesthesiologists; CVD, Cardiovascular diseases; RCRI, revised cardiac risk; BDZ, Benzodiazepine; IQR, Interquartil range
a- Pearson Chi-square test; b- Mann-Whitney U test; c- Fisher exact test;

emotional (ED), functional (FD) and cognitive.[38] Then, the postoperative value for each test is subtracted from the perioperative value, and if the difference is zero or equal, the patient is scored as recovered, existing a tolerance factor for the CD. To score as recovered, patients must recover in all domains.[39]

The research team also used the Portuguese version[40] of 15-item Quality of Recovery score (QoR-15), an instrument for the study of quality of recovery after anesthesia and surgery. The QoR-15 questionnaire has 15 questions that assess the patient-reported quality of postoperative recovery using a 0 (never/worst) to 10 (always/excellent) rating scale that leads to a minimum score of 0 (poor recovery) and a maximum score of 150 (excellent recovery).[40]

This questionnaire was applied to all patients before surgery (D0) and 24 hours after (D1), with the investigator asking the patient to rate, each one of the 15 items on the QoR-15.

We defined poor quality of recovery (PQR) for a QoR-15 score at day one (D1) lower than the mean QoR-15 score minus one SD.

Statistical analysis

Kolmogorov – Smirnov test for normality of the underlying variable was performed, and we used the Mann-Whitney U test, the chi-square and Fisher's exact test in the univariate analyses to compare continuous variables and proportions, respectively.

Data analyses were performed using Statistical Package for Social Sciences (SPSS) software for Windows version 24.0 (SPSS Inc, Chicago, IL, USA) and statistical significance was considered when p-value was < 0.05.

RESULTS

Of the 148 patients who were enrolled in the study, 23 (16%) developed POD. Patients' characteristics are at Table 1.

POD patients were older (73 vs 63 median ages, $p < 0.001$), had higher (III/IV) ASA-PS (61% vs 30%, $p = 0.004$), had a higher median Charlson comorbidity score (7 vs 5, $p = 0.045$), were more often submitted to major surgery (65% vs 35%, $p = 0.007$), had more heart failure (35% vs 7%, $p < 0.001$) and insulin-dependent diabetes mellitus (DM) (17% vs 3%, $p = 0.006$) having an higher (≥ 2) RCRI score (35% vs 14%, $p = 0.013$).

There were no significant differences between the two groups concerning sex, coronary heart disease, renal insufficiency and benzodiazepine use (pre-medication or medicated with).

In respect of quality of life before surgery (Table 2), POD patients had more problems in EQ-5D domains, with differences achieved in self-care problems (39% vs 11%, $p = 0.001$) and daily life activities (48% vs 26%, $p = 0.02$). POD patients had a similar prevalence of disability ($p = 0.095$) and frailty ($p = 0.138$).

Table 2. Quality of life before surgery: EuroQol 5 dimensions questionnaire (EQ-5D); disability and frailty scores

EQ-5D	n	POD (n=23)	NON-POD (n=125)	*p*
Mobility Problems	148			0.116[a]
Yes	44	10 (43%)	34 (27%)	
No	104	13 (57%)	91 (73%)	
Self-care	148			0.001[a]
Yes	23	9 (39%)	14 (11%)	
No	125	14 (61%)	111 (89%)	
Daily life activities Problems	147			0.02[a]
Yes	43	11 (48%)	32 (26%)	
No	104	11 (48%)	93 (74%)	
Pain/discomfort	148			0.558[a]
Yes	53	7 (30%)	46 (37%)	
No	95	16 (70%)	79 (63%)	
Anxiety/depression Problems	148			0.785[c]
Yes	117	19 (83%)	98 (78%)	
No	31	4 (17%)	27 (22%)	
Disability	148	8 (35%)	15 (12%)	0.095[a]
Frailty	148	10 (43%)	35 (28%)	0.138[a]

LEGENDA:
POD, Postoperative delirium; EQ-5D, EuroQol 5 dimensions questionnaire
a- Pearson Chi-square test; b- Mann-Whitney U test; c- Fisher exact test;

Concerning to type of anesthesia, there were no differences for POD patients (Table 1).

According to PQRS, POD patients had a minor rate of complete recovery at D1 for PD (50% vs 78 %, $p = 0.007$) and for FD (14% vs 36%, $p = 0.047$). Rates of recovery for EC, CD, and ND were similar in all time frames (Table 3).

Preoperative total score for QoR-15 was similar between POD patients (129 vs 130, $p = 0.270$) (Table 4).

Regarding QoR-15 at D1, POD patients had lower median total scores (91 vs 115, $p = 0.002$) and some items registered lower scores and statistically significant difference for those with POD: "been able to enjoy food" ($p = 0.004$), "able to look after personal toilet and hygiene unaided"($p = 0.003$), "able to communicate with friends" (p = 0.004), "moderate pain" ($p = 0.040$), "severe pain" ($p = 0.027$) and "feeling sad/ depressed" ($p = 0.022$) (Table 5).

At D1, POD patients had more frequently PQR (39% vs 10 %, $p = 0.002$), according to QoR-15 (Table 5).

POD patients had longer median surgery duration (160 vs 116 minutes, $p = 0.002$) and longer median length of stay at PACU (237 vs 128 minutes, $p = 0.004$) and at the hospital (8 vs 6 days, $p = 0.002$) (Table 1).

DISCUSSION

With this prospective observational study, we investigated

Table 3. Postoperative Quality of Recovery Scale (PQRS) after surgery at minute 15 (T15), 40 (T40) and days 1 (D1)

PQRS	n	POD (n=23)	NON-POD (n=125)	*p*
PD at T15	148	2 (8.7%)	16 (12.8%)	0.585[b]
PD at T40	148	4 (17%)	36 (29%)	0.385[b]
PD at D1	148	11 (48%)	94 (75%)	0.007[a]
ND at T15	148	15 (65%)	98 (78%)	0.173[a]
ND at T40	148	14 (61%)	90 (72%)	0.619[a]
ND at D1	148	21 (91%)	88 (70%)	0.400[a]
ED at T15	148	7 (30%)	43 (34%)	0.713[a]
ED at T40	148	2 (9%)	39 (31%)	0.142[b]
ED at D1	148	10 (44%)	46 (37%)	0.392[a]
CD at T15	148	1 (4%)	10 (8%)	0.541[b]
CD at T40	148	3 (13%)	20 (16%)	0.842[b]
CD at D1	148	2 (9%)	25 (20%)	0.276[b]
FD at T40	148	1 (4%)	26 (21%)	0.081[b]
FD at D1	148	3 (13%)	44 (35%)	0.038[b]

LEGENDA:
POD, Postoperative delirium; PD, Physiologic domain; ND, Nociceptive domain; ED, Emocional domain; CD, Cognitive domai
a- Pearson Chi-square test; b- Fisher exact test;

Table 4. Quality of recovery 15 (QoR-15) at D0

QoR-15 question at D0	POD (n=23)	NON-POD (n=125)	*p*
1. Able to breathe easily	10	10	0.212[a]
2. Been able to enjoy food	8	10	0.015[a]
3. Feeling rested	7	8	0.585[a]
4. Have had a good sleep	8	7	0.949[a]
5. Able to look after personal toilet and hygiene unaided	6	10	0.005[a]
6. Able to communicate with family or friends	9	10	0.005[a]
7. Getting support from hospital doctors and nurses	10	10	0.327[a]
8. Able to return to work or usual home activities	10	10	0.150[a]
9. Feeling comfortable and in control	9	9	0.210[a]
10. Having a feeling of general well-being	8	8	0.453[a]
11. Moderate pain	10	10	0.491[a]
12. Severe pain	10	10	0.366[a]
13. Nausea/ vomiting	10	10	0.068[a]
14. Anxiety	5	5	0.934[a]
15. Sad/ depressed	5	7	0.326[a]
Total Score, median (IQR)	129 (95-137)	130 (115-138)	0.270[a]

LEGENDA:
POD, Postoperative delirium; D0, preoperative; IQR, Interquartil range
a) Mann-Whitney U test;

Table 5. Postoperative Quality of recovery 15 (QoR-15) at D1

QoR-15 question D1	POD's group median score (n=23)	NON-POD group median score (n=125)	*p*
D1			
1. Able to breathe easily	10	10	0.164[a]
2. Been able to enjoy food	4	8	0.040[a]
3. Feeling rested	6	8	0.366[a]
4. Have had a good sleep	6	7	0.232[a]
5. Able to look after personal toilet and hygiene unaided	3	7	0.003[a]
6. Able to communicate with family or friends	10	10	0.004[a]
7. Getting support from hospital doctors and nurses	10	10	0.295[a]
8. Able to return to work or usual home activities	5	5	0.349[a]
9. Feeling comfortable and in control	7	8	0.165[a]
10. Having a feeling of general well-being	6	8	0.053[a]
11. Moderate pain	6	9	0.040[a]
12. Severe pain	9	10	0.027[a]
13. Nausea/ vomiting	10	10	0.494[a]
14. Anxiety	6	9	0.131[a]
15. Sad/ depressed	6	8	0.022[a]
Total Score, median (IQR)	91 (83-115)	115 (102-128)	0.001[a]
PQR	9 (39%)	13 (10%)	0.002[a]

LEGENDA:
POD, Postoperaive delirium; D1, postoperative day one; PQR, Poor quality of recovery; IQR, Interquartil range
a) Mann-Whitney U test;

the rates, characteristics, and impact of POD after cancer surgery. The principal findings of our study were as follows: a) after cancer surgery, the development of POD was a frequent event, with 16% of patients being affected; b) patients with POD were older, had higher rates of comorbidities, had a worse quality of life before intervention and were more frequently submitted to major surgery and; c) POD patients had a worse recovery after the procedure and presented more frequently with PQR and d) POD patients spent more time in the hospital.

In this study, we found a POD incidence of 16%. Between different oncological surgeries, we may find reports of a high range incidence. In a 2017 study, Park SA *et al,*[41] observed that 22.4% of patients who underwent liver resection developed delirium after surgery. This relatively higher incidence figure may be related to the fact that more complex types of surgery were included compared to our study. Others reported lower rates of POD after colorectal surgery for cancer treatment, Van der Sluis FJ *et al* reported rates of 10.3%[31] and Raats *et al,*[42] found an overall incidence of 21%, considering both urgent and elective surgeries (29% vs 18%).

The use of different diagnostic tools for POD may also contribute to the heterogeneity of POD incidence among studies.

Our results, including only scheduled interventions, are consistent with those of previous reports. Similar to other studies,[43-45] in this study, POD patients were older than those who did not develop POD.

Recently, in a study of head and neck surgery, Zhu Y *et al,*[45] demonstrated that advanced age was a significant risk factor for POD, and that age greater than 70 years old is an even more consistent risk factor.

Ageing and its inherent physical and functional decline have been the subject of study of several reports related to delirium. Many have advocated that, subjacent to an older age there is impairment of individual response to changes, such as those imposed by surgical stress. Therefore, it is thought that, with age, a stronger inflammatory response is activated during surgery, releasing a higher amount of cytokines and other inflammatory substances, which may diminish brain function.[27,31]

In a 2006 study on surgical trauma patients, Martin Hala *et al,*[30] concluded that many changes could lead to impairment of brain circulation, interfering with neuronal function, particularly in older individuals. Moreover, Capri M *et al,*[29] went further and, in a study of older patients, concluded that higher pre-operative levels of interleukin 6 (IL-6) in the blood can be related to POD onset.

In the present study, other POD patient characteristics included higher ASA-PS, higher frequency of cardiac disease and diabetes mellitus, and higher preoperative cardiac risk with an RCRI score ≥ 2. These data are consistent with previous research findings.[3,29,45,46]

In previous studies, as also found in this study, POD patients showed higher rates of other medical comorbidities. Accordingly, we can speculate that POD development after surgery may be related to worse baseline status and minor adjustment ability to new hemodynamic demands, such as surgery is.[31,44,45]

Patients who underwent major surgery had a higher risk of POD. As reported in the literature, extensive surgical intervention is associated with higher POD incidence, as shown in studies on delirium after radical cystectomy (29%),[43] or oesophagectomy (26%[5] and 50%[9]).

The role of benzodiazepines in POD development, particularly in ICU, have been widely studied([7-49] but as was also reported by other studies[50] we did not find an association between delirium development and benzodiazepines use. Pandharipande *et al,*[47] Pisani *et al,*[48] or Zaal *et al,*[49] discussed the use of benzodiazepines related to delirium development, in an ICU context. The results of these studies must be carefully considered, since, they involved critical care patients, using benzodiazepines for active sedation in a different environment. To the best of our knowledge, this association has been less studied in non-ICU context.

We found that patients having more problems with self-care or activities of daily living (ADL) more frequently developed POD, although they were not more disable or frail.

Although frailty and delirium share several commonalities, few studies have specifically focused on the relationship between frailty and delirium. We could not detect this relationship although, according to Rockwood *et al*,[51] it can be hypothesized that dependency accompanying delirium is a reflection of a whole-system failure and according to Jung *et al,*[52] frailty resulted in a 3- to 8-fold increase in the risk of postoperative delirium.

We cannot dissociate this result from a worse functional state before surgery, signifying higher ADL dependency. Other studies have found similar results and considered ADL dependency as a risk predictor for POD onset.[3,29]

The type of anesthesia, regional or general and its relation to POD have been the subject of numerous studies, with some of these studies reporting interesting results in minimizing delirium, through better management of the anesthesia procedure.[17,25]

We found no association concerning the type of anesthesia (general, regional, combined regional and general and analgesia and sedation). This agrees with other similar studies, providing support to the notion that general anesthesia does not increase POD rates.[46]

In contrast to other studies, we also examined how POD affects quality of recovery after surgery. To this end, we evaluated the effects of POD on quality of recovery, providing new information regarding POD progress. For that, we used valid and reliable scales,[34,37,40] applied by trained and specialized clinicians, enhancing results' veracity. To the best of our knowledge, this has not been previously studied or reported.

The evaluation of quality of recovery represents a paradigm shift for anesthesia changing the focus on outcomes to patient-centered outcomes. Using the QoR-15 and the PQRS we could look at a broad range of recovery domains in an objective fashion over repeated time periods identifying the impact of surgery and anesthesia on recovery in different aspects of recovery. We found that POD patients had a worst postoperative complete recovery in the physiological and functional domains of the PQRS. Additionally, they presented more frequently with PQR, according to the QoR-15 questionnaire. Moreover, after surgery, POD patients reported more pain and sadness/ feeling depressed and had lower total scores on the Qor-15, denoting a worse quality of recovery.

In a 2014 study, Kosar's team[32] investigated for the relation and impact of pain and depressive symptoms on POD risk, after orthopedic surgery. In their results, patients who had pain or were depressed before surgery were more predisposed to developing POD. In this respect, we could find that also after surgery, patients who had POD reported more pain and

feeling worse and more depressed.

As expected, POD patients had longer LOS at the hospital. They were also submitted to longer procedures and spent more time in the PACU. The results of other studies have shown that POD patients underwent longer surgeries and had prolonged postoperative LOS at the hospital. In fact, these have been described as strong factors that should alert to POD onset.[32,45,46]Gleason *et al,*[8] evaluated the association of major postoperative complications and delirium with adverse surgery outcomes. In that study, delirium was one of the major postoperative complications, playing an essential role in the incidence of adverse outcomes, such as hospital LOS, with delirium having a greater effect than other major complications. Therefore, we may consider that patients with delirium experience more difficulties during surgery recovery, being more susceptible to postoperative complications and longer hospital stay. Our study has some limitations. The first limitation is related to the use of the NuDESC: our results may have underestimated the rate of delirium incidence because the NuDESC is considered a screening tool. Moreover, the patients were evaluated only once at PACU discharge, and although widely used, the NuDESC does not allow the evaluation of POD severity; therefore we could not study severity and duration, which are important POD characteristics. Second, we could not differentiate among the types of delirium. This could be important, since, motor delirium subtypes can vary according to some characteristics, and these different characteristics can alert the clinician to pay greater attention to more common behaviours present in certain types of delirium, influencing treatment and final prognosis.[18] Third, this was a single-center study with a small sample size, resulting in limited power to identify differences and preventing the findings from being extrapolated, turning our results' generalization difficult.

CONCLUSION

In this study, POD was a frequent event after surgery, with 16% of patients being affected. Patients with POD were older, had higher ASA status (III/IV), higher RCRI scores, more frequently heart failure and insulin-dependent diabetes mellitus, were more frequently submitted to major surgery and had worse life quality before the intervention. POD patients had a worse recovery after the procedure, presented more frequently PQR and spent more time in the hospital.

AWARDS/PRESENTATIONS PRÉMIOS/APRESENTAÇÕES

The present study was based in the Master Thesis "Postoperative delirium after curative surgery for cancer" presented at Faculdade de Medicina do Porto by Pedro Miguel Fernandes Simões and supervised by Fernando José Abelha.

Conflitos de interesse
Os autores declaram não possuir conflitos de interesse.
Conflicts of interest
The authors have no conflicts of interest to declare.
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Confidencialidade de dados
Os autores declaram ter seguido os protocolos do seu centro de trabalho acerca da publicação dos dados de doentes.
Confidentiality of data
The authors declare that they have followed the protocols of their work center on the publication of data from patients.
Protecção de pessoas e animais
Os autores declaram que os procedimentos seguidos estavam de acordo com os regulamentos estabelecidos pelos responsáveis da Comissão de Investigação Clínica e Ética e de acordo com a Declaração de Helsínquia da Associação Médica Mundial.
Protection of human and animal subjects
The authors declare that the procedures followed were in accordance with the regulations of the relevant clinical research ethics committee and with those of the Code of Ethics of the World Medical Association (Declaration of Helsinki).

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