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ORIGINAL ARTICLE

Congestive heart failure as a determinant of postoperative delirium

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KEYWORDS
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Abstract
Background: Postoperative delirium (POD) is a frequent post-surgical complication that is associated with increased mortality and poor patient outcomes. POD is a complex disorder with multiple risk factors such as pre-existing patient comorbidities and perioperative complications. The aim of this study was to evaluate the incidence of POD and to identify risk factors for the development of POD in a post-anesthesia care unit (PACU).
Methods: We enrolled 97 adult patients admitted to a PACU over a five-day period (start date September 6, 2010). Patient demographics and intraoperative and postoperative data were collected. Patients were followed for the development of delirium using the Intensive Care Delirium Screening Checklist. Descriptive analyses of variables were used to summarize data, and the Mann–Whitney U test was used to compare continuous variables; the chi-square or Fisher's exact test was used for comparisons. Univariate analysis was performed using simple binary logistic regression with odds ratios (OR) and 95% confidence intervals (95% CI). The significance level for multiple comparisons was controlled by applying the Bonferroni correction for multiple comparisons and variables were deemed significant if $p \leq 0.0025$.
Results: Six percent of patients developed POD. These patients were older and more likely to have higher American Society of Anesthesiologists (ASA) physical status (83 vs. 22% with ASA III/IV, p=0.004) as well as a higher frequency of congestive heart failure (50 vs. 3%, p=0.003) and a higher Revised Cardiac Risk Index (RCRI) score (33 vs. 6% with RCRI ≥ 2, p=0.039). The duration of anesthesia for patients with POD was also longer and they received a greater volume of crystalloids, colloids, and erythrocytes during surgery. Congestive heart disease was an independent risk factor for POD (OR 29.3, 95% CI 4.1–210.6; p<0.001). In addition, patients who developed POD had higher in-hospital mortality and longer PACU and hospital stays.
Conclusions: Patients who developed POD had longer hospital and PACU stays and higher in-hospital mortality. Congestive heart disease was considered an independent risk factor for POD.

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PALAVRAS-CHAVE
Delirium pós-operatório;
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Complicações pós-operatórias

Insuficiência cardíaca congestiva como determinante de *delirium* pós-operatório

Resumo

Introdução: O *delirium* pós-operatório (DPO) é uma complicação frequente após a cirurgia. Está associado a um aumento da mortalidade e a piores resultados. O DPO é um distúrbio complexo, com múltiplos fatores de risco que incluem a existência de comorbilidades e complicações *per* operatórias. O objetivo deste estudo foi avaliar a incidência de DPO e identificar fatores de risco para o seu desenvolvimento numa unidade pós-anestésica.
Métodos: Foram incluídos no estudo 97 doentes adultos, internados na unidade de cuidados pós-anestésica (UCPA), após seis de setembro de 2010, durante um período de cinco dias. Foram registados dados demográficos, dados intraoperatórios e pós-operatórios. Os doentes foram seguidos para o desenvolvimento de *delirium* usando o *Intensive Care Delirium Screening Checklist*. Foi efetuada a análise descritiva para descrever as diferentes variáveis e o teste de Mann-Whitney foi utilizado para comparar variáveis contínuas; o teste do qui-quadrado ou o teste exato de Fisher foram usados para comparações. A análise univariada foi realizada por meio de regressão logística binária simples com *odds ratio* (OR) e seu intervalo de confiança de 95% (CI95%). O nível de significância para as comparações múltiplas foi controlado aplicando a correção de Bonferroni para comparações múltiplas e todas as variáveis foram consideradas significativas se $p \leq 0{,}0025$.
Resultados: Seis por cento dos doentes desenvolveram DPO. Os doentes que desenvolveram DPO eram mais velhos, tinham maior probabilidade de apresentar estado físico da *American Society of Anesthesiologists* (ASA) III/IV (83 *versus* 22%, p = 0,004), tinham insuficiência cardíaca congestiva em maior frequência (50 *versus* 3%, p = 0,003) e um maior *score* no *Revised Cardiac Risk Index* (RCRI) (33 *versus* 6% para RCRI ≥ 2, p = 0,039). Os doentes com DPO tiveram uma maior duração da anestesia e receberam um maior volume de cristaloides, coloides e eritrócitos durante a cirurgia. A doença cardíaca congestiva foi um fator de risco independente para DPO (OR 29,3, IC 95% 4,1-210,6, p < 0,001). Os doentes que desenvolveram DPO tiveram maior mortalidade hospitalar e maior tempo de internamento na UCPA e no hospital.
Conclusões: Os doentes que desenvolveram DPO tiveram maior tempo de internamento no hospital e na UCPA e tiveram maiores taxas de mortalidade hospitalar. A existência de doença cardíaca congestiva prévia foi considerado fator de risco independente para a ocorrência de DPO.

Introduction

Postoperative delirium (POD) is recognized as an important post-surgical complication. Delirium is defined as acute and fluctuating change of attention and cognition caused by a coexisting general medical condition.[1] It is more frequent among older adults.[2–4] Wide variations in POD incidence have been reported, from 5.1% to 52.2%.[2] This variability may be explained by differences in diagnostic criteria and study populations, as well as varying surgical procedures and differing methods of surveillance.

POD is not a benign syndrome[5]; it is associated with increased mortality and with poor patient outcomes.[4,6,7] It increases hospital length of stay (LOS) and hence hospital costs, and carries high postoperative complication rates. In addition, POD may be related to later functional and cognitive decline.[4,8–10] However, most strategies for dealing with POD are symptom-related only. Thus, prevention and early recognition are essential; it is vital to identify patients at risk to modify and control all possible modifiable risk factors.[11]

POD is a complex and heterogeneous disorder with multiple risk factors.[2,12] Comorbidities and perioperative conditions appear to be involved in its genesis,[13] and elderly patients are at greatest risk.[2,14] Higher rates of POD are also seen in patients with impaired mobility,[10] comorbidities (American Society of Anesthesiologists [ASA] ≥3),[2,5,10,14,15] and lower cognitive function or reduction in sensory function.[4,16,17] The incidence of POD may be higher in patients taking benzodiazepines preoperatively,[15] and preoperative pain may increase the risk of POD.[18] Other possible risk factors have been reported, among them a history of alcohol abuse and chronic narcotic use.[4,16] Recently, Radtke et al.[14] reported that preoperative fluid fasting exceeding six hours was an independent risk factor for POD.

Perioperative conditions can also have a pronounced impact on POD, and major surgery is a known risk factor[19] including cardiac surgery,[20,21] non-cardiac thoracic procedures,[14,22] and intra-abdominal surgery,[14] but emergency procedures also raise the risk.[8] Pain, blood loss, hemodynamic changes, and exposure to medications are potential risk factors.[12,23] Hematocrit <30% has also been reported as a risk factor for POD.[22] However, there appears to be no difference in risk level between general or local and regional anesthesia.[18,24] Duration of mechanical ventilation has also been identified as an independent predictor of POD.[21]

Postoperative factors are also important. One of the key factors is pain control, because acute pain is associated with POD.[5,9,13,18,25,26] Early development of POD in the recovery room predicts later POD occurrence in the ward.[14]

The risk of POD increases with each additional risk factor.[10,14] As populations age, the number of older surgical patients is set to rise, and POD is likely to remain a common condition.[10,15,18,27]

The aim of this study was to evaluate the incidence of POD in a post-anesthesia care unit (PACU) and to identify risk factors for the development of POD.

Methods

Patient selection

The institutional review board and the Ethics Committee of Hospital de São João approved this study and informed consent was obtained preoperatively from all study participants. This prospective study was carried out in the multidisciplinary PACU at Hospital São João, a 1100-bed community teaching hospital in Porto, Portugal. All patients admitted to the PACU over a five-day period (start date September 6, 2010) were evaluated. The inclusion criteria were adult Portuguese-speaking patients undergoing major elective non-cardiac and non-neurological surgery who required anesthesia for which they were expected to remain in the hospital postoperatively for more than 48 hours. We excluded patients who did not provide or were incapable of providing informed consent, and those with a history of central nervous system disease, Parkinson's disease, neurological or cardiac surgery, delirium, or use of antipsychotic medication.

Patient assessment

The following variables were recorded on admission to the PACU: age, gender, temperature, body mass index, fasting time before surgery, and anesthesia-related data (specifically duration and type of anesthesia, and fluids and blood products used).

We calculated the patients' Revised Cardiac Risk Index (RCRI) scores as described by Lee et al.,[28] assigning 1 point for each of the following risk factors: high-risk surgery, ischemic heart disease, cerebrovascular disease, diabetes requiring insulin therapy, and renal failure.

In accordance with Lee et al.,[28] patients were considered to have a history of ischemic heart disease if they had a history of myocardial infarction, had current positive exercise test or ischemic chest pain, used nitrate therapy, or had an ECG with pathological Q waves. A history of congestive heart failure included patients with a history of heart failure, pulmonary edema, or paroxysmal nocturnal dyspnea. Congestive heart failure was also considered present if physical examination revealed bilateral rales or S3 gallop, or if a chest radiograph revealed pulmonary vascular redistribution. Cerebrovascular disease was defined as a history of transient ischemic attack or stroke.

PACU data, hospital LOS, and in-hospital mortality were also recorded for all patients.

Evaluation of delirium

Each patient included in the study was evaluated for delirium using the Intensive Care Delirium Screening Checklist (ICDSC).[29] According to the ICDSC, patients are defined as having developed delirium if they have a test score of 4 or more points.

Trained research assistants assessed patients in the recovery room after patients were formally declared 'ready for discharge' by the anesthesiologist in charge of the recovery room. The research team did not interfere with the typical recovery room protocol, and recovery room physicians and nurses were blinded to all study results. Regular recovery room staff did not diagnose delirium for any of the patients in this study.

Statistical analysis

Descriptive analyses of variables were used to summarize data, and the Mann–Whitney U test was used to compare continuous variables; the chi-square or Fisher's exact test was used to compare proportions between the two subject groups (POD vs. non-POD).

Univariate analysis was performed to evaluate the determinants of POD; these comprised simple binary logistic regression with odds ratios (OR) and 95% confidence intervals (95% CI) and were carried out for the following independent variables: age, gender, body mass index, ASA physical status (ASA-PS), comorbidities and RCRI score, type and duration of anesthesia, intraoperative fluid administration, and body temperature at PACU admission.

To reduce the risk of type II error, the significance level for multiple comparisons was controlled by applying the Bonferroni correction for multiple comparisons (test-wise significance level divided by the number of tests performed). Variables were deemed significant if $p \leq 0.0025$. Data were analyzed using SPSS for Windows version 19.0 (SPSS, Chicago, IL, USA).

Results

We screened 105 patients who were admitted to the PACU during the study period. Four patients were excluded because of history of central nervous system disease; two were excluded because of delirium and antipsychotic medication; one because he did not speak Portuguese; and one because he had undergone neurosurgery.

Thus, 97 patients were included in the study. The baseline characteristics of all patients are listed in Table 1. Patients' median age was 56 years (range, 18–82 years), with 71% of subjects aged less than 65 years. The gender proportions were similar (45% men and 55% women). Forty-five percent of patients underwent general surgery, 14% had orthopedic surgery, 12% urological surgery, and 11% vascular surgery; the remaining patients underwent plastic and reconstructive surgery, or gynecological procedures. Of these, 37% were classified as high-risk surgery.

Overall, six of the 97 patients (6.2%) developed delirium during their PACU stay. Table 2 shows the measured variables comparing patients who developed POD with those who did not. Patients who developed delirium were older (median 71

Table 1 Patient characteristics.

Variable	All (n=97)
Age in years, median (IQR)	56 (48–67)
Age group, n (%)	
≥65 years	28 (29)
<65 years	69 (71)
Gender, n (%)	
Male	44 (45)
Female	53 (55)
ASA physical status, *n (%)*	
I/II	72 (74)
III/IV	25 (26)
Body mass index in kg/m², median (IQR)	26 (23–30)
Hypertension, n (%)	59 (61)
COPD, n (%)	3 (3)
High-risk surgery, n (%)	36 (37)
Ischemic heart disease, n (%)	9 (9)
Congestive heart disease, n (%)	6 (6)
Cerebrovascular disease, n (%)	5 (5)
Renal failure, n (%)	6 (6)
Insulin therapy for diabetes, n (%)	9 (9)
Total RCRI, n (%)	
≤2	89 (92)
>2	7 (8)

ASA: American Society of Anesthesiologists; CI: confidence interval; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; PACU: post-anesthesia care unit; RCRI: Revised Cardiac Risk Index.

years vs. 55 years, p=0.008), had higher ASA-PS scores (83% vs. 22% with ASA III/IV, p=0.004) and longer duration of anesthesia (median 225 min vs. 120 min, p=0.012), were more likely to have a history of congestive heart failure (50% vs. 3%, p=0.003), had higher RCRI scores (33% vs. 6% with RCRI ≥2, p=0.039), and had a higher use of crystalloids (median volume, 3000 ml vs. 1000 ml, p<0.001), colloids, and erythrocytes. There were no significant differences in the type of anesthesia used (local and regional vs. general) or in preoperative fasting time (median 14.5 hours vs. 14.0 hours, p=0.730).

Patients who developed POD had longer PACU LOS (median duration, 540 min vs. 95 min, p=0.002) and hospital LOS (median duration, 22 days vs. 3 days, p=0.003); they also had higher in-hospital mortality (33% vs. 1%, p=0.009).

Simple binary logistic regressions were used to examine the covariate effects of each factor on POD development (Table 3); this was done using a significance level of p≤0.0025, and our analysis showed that congestive heart disease was an independent risk factor for POD (OR 29.3, 95% CI: 4.1–210.6; p<0.001).

Discussion

To the best of our knowledge, this is the first study to show that congestive heart failure is an independent risk factor for POD. The main finding of our study is that patients who develop POD more often have congestive heart failure and that this condition may be a risk factor for POD. Hutt et al.[30] reported a higher prevalence of delirium in patients with heart failure (35.3% of 156 patients in a nursing home); that study also found an association with a 3-fold increase in 60-day mortality. Furthermore, a study by Uthamalingam et al.[31] investigating a congestive heart disease population also demonstrated that delirium was independently associated with increased 30- and 90-day readmission and short-term mortality after adjusting for potential confounders; these authors did not, however, demonstrate that congestive heart disease was a risk factor for delirium.

In the study by Uthamalingam et al.,[31] delirium was associated with increased heart rate, increased serum B-type natriuretic peptide levels, and increased rales in the lung base, all of which are associated with activation of the sympathetic nervous and renin–angiotensin systems, and with increased release of cytokines. This presentation observed in delirious patients stemming from increased angiotensin and aldosterone may impair cerebral metabolism and perfusion and thus help explain the pathophysiology of delirium in patients with congestive heart failure.

POD is thought to be the result of an interaction between multiple risk factors.[2,10,12] Some authors have reported an incidence as high as 60%.[9] However, although we used the ICDSC, a highly sensitive delirium screening tool, we still only determined a POD incidence of 6.2%; this is slightly lower than found by other authors.[4,6,7,10,14,16,22] The lower incidence in our study may be explained by the use of the ICDSC, which some claim is less sensitive than other screening tools.[32] Although the ICDSC is less sensitive than other methods for delirium screening, we used it because of its user-friendly checklist which is easy to administer in environments with relatively high patient flow; the ICDSC also has high sensitivity and reliability and can be completed rapidly.[33]

Another possible cause of the low POD incidence in our study is the demographic characteristics of our study population, with a higher proportion of younger patients and better preoperative status (patients with lower ASA-PS and lower RCRI). Surgical factors may also have contributed to this lower incidence because all of our patients underwent scheduled surgery and only 37% of the procedures were classified as high risk. Additionally, we excluded all patients undergoing cardiac and neurological surgery from this study, and these procedures are frequently associated with higher POD incidence.[2,20–22]

This study compared patients who developed POD with those who did not. As in previous studies, we found that delirious patients were older than non-delirious patients. In addition, patients with congestive heart disease had a higher risk of developing POD, and our study showed that congestive heart disease was independently associated with POD (OR 29.3). These patients have lower cardiac reserve; this could have led to a higher risk of intraoperative hemodynamic complications and may have contributed to POD development. The majority (83%) of patients who developed POD in our study had an ASA-PS of III/IV, in contrast with only 22% of the non-delirious patients. Thus it appears that worse ASA status may lead to a higher risk of developing POD.

Although we did not distinguish between fluid and solid fasting in our study, we found no significant difference in the

Table 2 Delirium vs. non-delirium characteristics and outcome.

Variable	Non-delirium (n=91)	Delirium (n=6)	p
Age in years, median (IQR)	55 (47–66)	71 (64–75)	0.008[a]
Age group, n (%)			0.056[b]
<65 years	67(74)	2 (33)	
≥65 years	24 (26)	4 (67)	
Gender, n (%)			0.569[b]
Male	41(45)	3 (50)	
Female	50 (55)	3 (50)	
ASA physical status, n (%)			0.004[b]
I/II	71 (78)	1 (17)	
III/IV	20 (22)	5 (83)	
Body mass index in kg/m^2, median (IQR)	26 (23–30)	26 (25–30)	0.505[a]
Duration of anesthesia (min), median (IQR)	120 (70–180)	225 (143–480)	0.012[a]
Type of anesthesia, n (%)			0.763[b]
General/combined general and local and regional	71 (78)	5 (83)	
Local and regional	20 (22)	1 (17)	
Temperature at PACU admission, median (IQR)	35.0 (34.5–35.5)	34.7 (34.1–35.9)	0.559[a]
Hypertension, n (%)	54 (59)	5 (83)	0.238[b]
COPD, n (%)	2 (2)	1 (17)	0.176[b]
High-risk surgery, n (%)	32 (35)	4 (67)	0.124[b]
Ischemic heart disease, n (%)	7(8)	2 (33)	0.095[b]
Congestive heart disease, n (%)	3 (3)	3 (50)	0.003[b]
Cerebrovascular disease, n (%)	4 (4)	1 (17)	0.452[b]
Renal failure, n (%)	5 (6)	1 (17)	0.325[b]
Insulin therapy for diabetes, n (%)	8 (9)	1 (17)	0.561[b]
Total RCRI, n (%)			0.039[b]
≤2	87 (96)	5 (83)	
>2	4 (4)	1 (17)	
Crystalloids, median (IQR)	1000 (1000–2000)	3000 (2300–4125)	<0.001[a]
Colloids, median (IQR)	0 (0–0)	0 (0–125)	0.049[a]
Erythrocytes, median (IQR)	0 (0–0)	0 (0–2)	<0.001[a]
Platelets, median (IQR)	0 (0–0)	0 (0–0)	1[a]
Fasting time (hours), median (IQR)	14.0 (10.1–16.0)	14.5 (12.8–15.4)	0.730[a]
PACU length of stay (hours), median (IQR)	95 (69–141)	540(331–540)	0.002[a]
Hospital length of stay (days), median (IQR)	3 (2–8)	22 (12–125)	0.003[a]
In-hospital mortality, n (%)	1 (1)	2 (33)	0.009[b]

[a] Mann–Whitney U test.
[b] Fisher's exact test. ASA: American Society of Anesthesiologists; CI: confidence interval; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; PACU: post-anesthesia care unit; RCRI: Revised Cardiac Risk Index.

risk of POD development and fasting time between the POD and non-POD groups; this differs from the results of Radtke et al.,[14] who concluded that the duration of preoperative fluid fasting was an independent risk factor for POD.

On the other hand, the results of the present study agreed with those of earlier studies in that we failed to find any significant differences in POD development according to the type of anesthesia used (local and regional vs. general).[18,24] However, patients who developed POD in our study had a longer duration of anesthesia, which may be explained by the need for longer anesthesia in cases of prolonged surgery. This in turn can be considered a possible indicator of increased operative complexity and of a higher risk of neurological complications.[20]

Dehydration has been labeled a risk factor for POD.[34] In this study, delirious patients received greater volumes of crystalloids, colloids, and erythrocytes than non-delirious patients. However, there may have been an observation bias in the present study, because the worse the general condition of a patient, the higher the volumes needed to stabilize that patient.

As reported by other authors, our findings demonstrated that patients who developed delirium had longer stay in both the PACU and the hospital, and also had higher in-hospital mortality.[4,8,9] This indicates that POD leads to more post-surgical complications and worse outcomes.

This study has several limitations. First, the number of patients included in our analysis was low; the sample may

Table 3 Univariate analysis for determinants of delirium.

Variable	Delirium/non-delirium (n=91)/(n=6)	Odds ratio (95% CI)	p
Age in years, median (IQR)	71 (64–75)/55 (47–66)	1.11 (1.01–1.21)	0.028
Gender, n (%)			0.814
Male	3 (50)/41(45)	1.22 (0.23–6.64)	
Female	3 (50)/50 (55)	1	
ASA physical status, n (%)			0.011
I/II	1 (17)/71 (78)	1	
III/IV	5 (83)/20 (22)	17.75 (1.96–160.77)	
Body mass index in kg/m^2, median (IQR)	26 (25–30)/26 (23–30)	1.02 (0.90–1.15)	0.786
Duration of anesthesia (min), median (IQR)	225 (143–480)/120 (70–180)	1.00 (1.00–1.01)	0.050
Type of anesthesia, n (%)			0.761
General/combined general and local and regional	5 (83)/71 (78)	1.41 (0.16–12.76)	
Local and regional	1(17)/20 (22)	1	
Temperature at PACU admission, median (IQR)	34.7 (34.1–35.9)/35.0 (34.5–35.5)	0.82 (0.29–2.32)	0.703
Hypertension, n (%)	5 (83)/54 (59)	3.43 (0.38–30.53)	0.270
COPD, n (%)	1 (17)/2 (2)	8.90 (0.69–115.58)	0.095
High-risk surgery, n (%)	4 (67)/32 (35)	3.69 (0.64–21.24)	0.144
Ischemic heart disease, n (%)	2 (33)/7(8)	6.00 (0.93–38.71)	0.060
Congestive heart disease, n (%)	3 (50)/3 (3)	29.33 (4.09–210.57)	0.001
Cerebrovascular disease, n (%)	1 (17)/4 (4)	4.35 (0.41–46.51)	0.224
Renal failure, n (%)	1 (17)/5 (6)	3.44 (0.34–35.31)	0.298
Insulin therapy for diabetes, n (%)	1 (17)/8 (9)	2.08 (0.22–20.01)	0.528
Total RCRI, n (%)			0.028
≤2	5 (83)/87 (96)	1	
>2	1 (17)/4(4)	8.60 (1.26–58.78)	
Crystalloids, median (IQR)	3000 (2300–4125)/1000 (1000–2000)	1.00 (1.00–1.00)	0.003
Colloids, median (IQR)	0 (0–125)/0 (0–0)	1.00 (1.00–1.01)	0.095
Erythrocytes, median (IQR)	0 (0–2)/0 (0–0)	1.00 (1.00–1.01)	0.048
Fasting time (hours), median (IQR)	14.5 (12.8–15.4)/14.0 (10.1–16.0)	0.99 (0.91–1.07)	0.773

ASA: American Society of Anesthesiologists; CI: confidence interval; COPD: chronic obstructive pulmonary disease; IQR: interquartile range; PACU: post-anesthesia care unit; RCRI: Revised Cardiac Risk Index.

be too small to draw statistically significant conclusions. This small sample size may also be linked to another important limitation, in that only a small number of patients with a prior history of congestive heart disease were included. This is even more important given that congestive heart disease was considered an independent risk factor for delirium. It should also be taken into account that the patients studied were not critical care patients. However, despite our relatively small sample size, the percentage of patients with postoperative delirium was similar to the percentages seen in other studies involving patients undergoing major surgery.[29]

Another limitation of our study is that the patients were screened for delirium only in the PACU and many of these patients stayed in this unit for a short time only. As a result, we may have missed delirium which developed at a later stage. Some authors have stated that most cases of POD arise on the second day after surgery.[4,35]

POD can be prevented in some patients, and prevention programs have been applied with some success.[19] It is important for hospital teams to be aware of the need for screening and prevention of POD. This study adds to the growing body of evidence demonstrating that POD is an important post-surgical complication and one that can result in worse outcomes for surgical patients. We also found that congestive heart disease was an independent risk factor for POD. In addition, POD appears to be more common in older patients and in patients with worse ASA-PS and worse RCRI scores. Longer anesthesia times, major surgery, and the presence of comorbidities may all increase the risk of POD.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data and that all the patients included in the study received sufficient information and gave their written informed consent to participate in the study.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author is in possession of this document.

Conflicts of interest

The authors have no conflicts of interest to declare.

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