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ORIGINAL ARTICLE

Apolipoprotein E e4 allele does not increase the risk of early postoperative delirium after major surgery

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Abstract
Background A relationship between patients with a genetic predisposition to and those who develop postoperative delirium has not been yet determined. The aim of this study was to determine whether there is an association between apolipoprotein E epsilon 4 allele (*APOE4*) and delirium after major surgery.
Methods Of 230 intensive care patients admitted to the post anesthesia care unit (PACU) over a period of 3 months, 173 were enrolled in the study. Patients' demographics and intra- and postoperative data were collected. Patients were followed for the development of delirium using the Intensive Care Delirium Screening Checklist, and DNA was obtained at PACU admission to determine apolipoprotein E genotype.
Results Fifteen percent of patients developed delirium after surgery. Twenty-four patients had one copy of *APOE4*. The presence of *APOE4* was not associated with an increased risk of early postoperative delirium (4% vs. 17%; $P = 0.088$). The presence of *APOE4* was not associated with differences in any studied variables. Multivariate analysis identified age [odds ratio (OR) 9.3, 95% confidence interval (CI) 2.0–43.0, $P = 0.004$ for age $\geq$65 years), congestive heart disease (OR 6.2, 95% CI 2.0–19.3, $P = 0.002$), and emergency surgery (OR 59.7, 95% CI 6.7–530.5, $P < 0.001$) as independent predictors for development of delirium. The Simplified Acute Physiology Score II (SAPS II) and The Acute Physiology and Chronic Health Evaluation II (APACHE II) were significantly higher in patients with delirium ($P < 0.001$ and 0.008, respectively). Hospital mortality rates of these patients was higher and they had a longer median PACU stay.
Conclusions Apolipoprotein e4 carrier status was not associated with an increased risk for early postoperative delirium. Age, congestive heart failure, and emergency surgery were independent risk factors for the development of delirium after major surgery.

Keywords Apolipoprotein E epsilon 4 allele · ICDSC · Delirium · Intensive care

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Background

Postoperative delirium is associated with a poor outcome, including increased length of hospital and intensive care unit (ICU) or post anesthesia care unit (PACU) stay, frequent medical complications, and increased mortality risk [1–6]. Delirium is often the first presenting feature of physical illness or drug toxicity, and failing to recognize it may lead to delay in diagnosing and treating the underlying cause [7]. Early identification and treatment of delirium is the key to reducing its duration, severity, and negative

outcomes [7–9]. Despite the high prevalence of delirium among critical ill patients and its clinical importance, no specific etiologic factor has been identified [10]. As not all patients with similar risk factors and similar conditions develop delirium, it may be thought that genetic variation may be a risk factor [10–12]. Common pathophysiological pathways for dementia and delirium, such as B-amyloid plaque formation, increased inflammation, and reduced cholinergic activity in the brain, may predispose patients with pre-existing cognitive impairment to development of delirium [10, 13–15]. Because apolipoprotein E (APOE) plays a role in all these mechanisms, an association between APOE and delirium can also be hypothesized [11, 12].

Apolipoprotein E (*APOE* gene; ApoE protein) is a 299-amino-acid lipid-binding protein with multiple biological properties. There are three common human isoforms of apoE, designated apoE2, apoE3, and apoE4, which differ by single amino-acid interchanges at residues 112 and 158 [16]. APOE is involved in mobilization and redistribution of cholesterol in repair, growth, and maintenance of myelin and neuronal membranes during development or after injury [17], so it is important in recovery after neuronal damage. The epsilon 4 allele of the *APOE* gene has been shown as a risk factor for Alzheimer's disease [18], poor outcome after closed head injury and intracranial hemorrhage [19, 20], and accelerated cognitive decline with normal aging. Whether patients who subsequently develop postoperative delirium have a genetic predisposition risk factor has been the subject of various studies. Some of these studies found no association between the APOE epsilon 4 (*APOE4*) allele and delirium; others found a correlation between *APOE4* and a longer duration of delirium [10, 11, 18–20]. The aim of this study was to determine whether or not there is an association between *APOE4* and delirium after major surgery.

Material and methods

The institutional review board and the ethics committee approved the study, and informed consent was obtained preoperatively from each studied patient. This prospective study was carried out in the multidisciplinary PACU with five intensive care beds at the Hospital São João, a 1,100-bed community teaching hospital in Porto, Portugal. All consecutive adult Portuguese-speaking patients admitted to the five ICU beds of the PACU after major elective non-cardiac and nonneurological surgery requiring anesthesia and who were expected to remain in the hospital postoperatively for >48 h (definition of major surgery) between 1 April 2009 and 31 July 2009 where eligible for the study. Patients who did not 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 antipsychotic medication, or drug, alcohol, or opioid abuse were excluded. The following variables were recorded on admission to the PACU: age, gender, body mass index (BMI), preadmission comorbidities (specifically, ischemic heart disease, congestive heart failure, cerebrovascular disease, hypertension, renal insufficiency, diabetes, hyperlipidemia) and anesthesia data (specifically, duration, type of anesthesia, fluids and blood products used). PACU data, hospital length of stay (LOS), and mortality were also recorded for all patients. The Acute Physiology and Chronic Health Evaluation (APACHE) II [21] and the Simplified Acute Physiology Score II (SAPS II) [22] were calculated using standard methods. Using the classification developed by Lee et al. [23], we calculated the Revised Cardiac Risk Index (RCRI), assigning one point for each of the following risk factors: high-risk surgery, ischemic heart disease, cerebrovascular disease, diabetes mellitus requiring insulin therapy, and renal failure. Physiologic data were recorded using customized data. Serum creatinine and troponin I (cTnI) were also recorded on admission and each day in tjhe PACU.

Functional capacity

Functional capacity before surgery was evaluated in terms of the patient's ability to handle personal and instrumental activities of daily living (ADL) within the first 24 h after PACU admission. All eligible consenting patients were interviewed directly by a trained investigator. When the patient was unable to respond, the questionnaire was completed by a close family member living in the same household as the patient. The questionnaire used to assess dependency was based on the Katz Index of Independence in ADL [24] and Lawton's Instrumental Activities of Daily Living scale [25]. The Lawton I-ADL scale is an easily administered assessment instrument that provides self-reported information about the functional skills necessary for living in the community. Deficits in the instrumental Lawton scale were scored, and a summary score ranging from 0 (low function, dependent) to 7 (high function, independent) was obtained. The Katz ADL scale assesses basic personal ADL and ranks adequacy of performance in six functions. Dependency in each personal activity was evaluated, and a summary score ranging from 0 (independence in all activities) to 6 (dependency in all activities) was obtained. The personal ADL (P-ADL) considered were bathing, dressing, going to the toilet, transferring from bed to chair, continence, and feeding. The instrumental ADL (I-ADL) considered were housekeeping, food shopping, using transportation, preparing food, using the telephone, and handling medications and finances. Answers were categorized into two groups: able or unable to perform each

activity and group of activities. Patients were considered dependent if they were dependent in at least one I-ADL or P-ADL.

Postoperative complications

Postoperative occurrence of major cardiac events (MCE) was recorded. Acute myocardial infarction, pulmonary edema, ventricular fibrillation, or primary cardiac arrest and complete heart block were recorded during PACU stay and considered to be MCE. Acute myocardial infarction was diagnosed according to the criteria of the European Society of Cardiology/American College of Cardiology [26]. At admission to and every day in the PACU, samples for creatine kinase-MB (CK-MB) and cTnI were collected from all patients, and 12-lead electrocardiogram (ECG) was performed whenever symptoms of myocardial events occurred. All patients had continuous acquisition of leads II and V ECG to identify and diagnose possible arrhythmias. Postoperative occurrence of acute kidney injury (AKI) was recorded using the proposed definition by the Acute Kidney Injury Network (AKIN) [27]. The diagnostic criteria require a 0.3 mg/dl or $\geq$50% change in serum creatinine (sCr) from baseline or a reduction on urine output of $<$0.5 ml/kg/h over a 6-h interval within a 48-h period following adequate volume resuscitation.

Length of stay and mortality

We also recorded PACU and hospital LOS. For mortality, we registered PACU and hospital mortality and mortality at 6 months after PACU discharge.

Genotyping of *APOE4* allele

DNA for genotyping was extracted from whole blood using a MagnaPure LC system (Roche Applied Science, Indianapolis, IN, USA) that was prospectively collected on the day of study enrollment. APOE genotype determinations were performed using polymerase chain reaction (PCR) amplification, followed by sequencing using the ABI Prism Dye Terminator Cycle Sequencing kit (Applied Biosystems, Foster City, CA, USA) and an Applied Biosystems 3130xl Genetic Analyzer. To detect the *APOE4* allele, PCR amplifications were performed in a 25-µl volume containing 200 µM of each deoxyribonucleotide triphosphate (dNTP), 20 pmol of each of the forward and reverse primers, 50 mM calcium chloride (KCl), 10 mM Tris–hydrochloric acid (HCl) (pH 9.0), 1.5 mM magnesium chloride ($MgCl_2$) and 1 U of Taq DNA polymerase (Qiagen, Valencia, CA, USA). Cycling conditions were 30 s at 94°C, 30 s at 57°C, and 30 s at 72°C for 30 cycles. Primer sequences were as follows: forward, 5′-TCGGAACTG GAGGAACAACT-3′; reverse, 5′-GCGCTTCTGCAGGT CATC-3′.

Delirium evaluation

Each patient admitted to PACU and included in the study was evaluated for diagnosis of delirium using the Intensive Care Delirium Screening Checklist (ICDSC) administered within 24 h of admission and then every 8 h [28]. According to the ICDSC, a patient was defined as a delirium-positive if their test score was $\geq$4 points in any evaluation.

Statistical method

Descriptive analyses of variables were used to summarize data and the Mann–Whitney *U* test was used to compare continuous variables; chi-square or Fisher's exact test were used to compare proportions between two groups of subjects. To evaluate the determinants of postoperative delirium, univariate analysis was performed using simple binary logistic regression with an entry criterion of $P \leq 0.05$ with the following variables: age, gender, BMI, American Society of Anesthesiologists Physical Status (ASA-PS), type and magnitude of surgery, co-morbidities, RCRI score, type of anaesthesia, length of anaesthesia, temperature at admission to the PACU, troponin I at admission, dependency on ADL, SAPS II, PACU and hospital mortality and LOS. All the preadmission variables deemed significant ($P \leq 0.05$) were incorporated into multiple regression binary logistic analyses with forward conditional elimination to examine covariate effects of each factor on delirium development. All variables deemed to be significant ($P \leq 0.05$) were established as independent predictors of postoperative delirium. The odds ratio (OR) and its 95% confidence interval (CI) were calculated. Data were analyzed using SPSS for Windows version 17.0 (SPSS, Chicago, IL, USA).

Results

There were 230 adult PACU admissions during the study period. Fourteen patients were excluded because they were submitted to neurosurgical surgery, eight were admitted more than once to the PACU, two were younger than 18 years, one did not speak Portuguese, one refused to participate, one had Parkinson's disease, three were admitted with a diagnosis of delirium or had antipsychotic medication, and three abused alcohol or drugs. In six patients, it was never possible to evaluate delirium with the ICDSC, and we had no genetic study for 24 patients. General surgery and vascular procedures represented a

Table 1 Surgical procedure ($n = 173$)

Procedure	Number (%)
Gastrointestinal	74 (43)
Vascular	36 (21)
Orthopaedic	21 (12)
Urology	17 (10)
Plastic and reconstructive	9 (5)
Gynecologic	6 (4)
Head and neck	4 (2)
Thoracic	2 (1)
Otorhinolaryngology	2 (1)
Obstetrics	2 (1)

significant proportion of the total number of patients (Table 1).

The characteristics of patients with and without postoperative delirium are summarized in Table 2. Univariate analysis identified the following independent predictors for development of postoperative delirium: age (median 75 vs. 61 years, $P < 0.001$), ASA physical status (89% vs. 61% were ASA-PS III/IV, $P = 0.007$), emergency surgery (23% vs. 5%, $P = 0.002$), hyperlipidemia (65% vs. 35%, $P = 0.004$), troponin I at admission (3.3 ± 16.6 vs. 0.02 ± 0.03, $P = 0.005$), ischemic heart disease (46% vs. 13%, $P < 0.001$), congestive heart disease (65% vs. 25%, $P < 0.001$), RCRI scores (42% vs. 12% had RCRI >2), and scores in Lawton scale of P-ADL (5.1 ± 2.6 vs. 6.3 ± 1.8, $P = 0.004$) and dependency in P-ADL (44% vs. 17%, $P = 0.004$).

Table 3 shows the severity of disease scores, complications, and outcome. Patients with postoperative delirium were more severely ill (median SAPS II 26 vs. 18, $P < 0.001$ and median APACHE II 9 vs. 8, $P = 0.008$) and stayed longer at the PACU (median LOS 46 h vs. 19 h, $P < 0.001$). The unadjusted mortality rate at 6 months follow-up of patients with postoperative delirium was 39%, nearly eight times the mortality rate of those without postoperative delirium (39% vs. 5%, $P < 0.001$). The increased mortality rate observed among patients with postoperative delirium was even greater for hospital mortality rate (35% vs. 3%, $P < 0.001$).

The occurrence of postoperative AKI was higher in patients who developed postoperative delirium (27% vs. 6%, $P = 0.001$) but not for patients who developed MCE (8% vs. 1%, $P = 0.108$). Multiple regression logistic analysis was used to examine covariate effects of each factor on postoperative delirium development (Table 4). In this analysis, the regression model included all variables that showed statistical significance in the univariate analysis made for determinants of postoperative delirium development. This analysis showed that significant risk factors for postoperative delirium were age (OR 9.30, 95% CI 2.01–43.03, $P = 0.004$), emergency surgery (OR 59.73, 95% CI 6.72–530.48, $P < 0.001$), and congestive heart disease (OR 6.21, 95% CI 1.99–19.33, $P = 0.002$).

Of the 173 patients studied, 24 (14%) had at least one copy of the *APOE4* allele. The presence of one copy was not associated with postoperative delirium (4% vs. 17%, $P = 0.088$) (Table 5).

The presence of at least one copy of the *APOE4* allele was not associated with differences in the studied variables, in the frequency of postoperative complications, and in outcome.

Discussion

Given the high prevalence of delirium among critical ill patients and the negative clinical outcome associated with it, current practice guidelines recommend that ICU patients should be routinely screened for delirium using a validated screening tool [29]. The ICDSC, created in 2001 by Bergeron et al. [28] comprises eight items based on the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) criteria and features of delirium, including inattention, disorientation, hallucination–delusional psychosis, psychomotor agitation or retardation, inappropriate speech or mood, sleep/wake cycle disturbances, and symptom fluctuation according to a total score system from 0 to 8 points. The development of delirium is thought to be dependent on the combination of a multifactorial process in which there is an interrelationship between baseline patient vulnerability and precipitating factors or insults [30]. Studies of factors thought to be part of the universe of baseline characteristics have led to a multiplicity of studies about genetic precipitating factors.

In this study, although we used ICDSC, a very sensitive tool for screening delirium, the incidence of postoperative delirium in PACU after major surgery was 15%. This relative lower percentage of postoperative delirium is even higher than that described by others in a PACU [31, 32] and occurs after a very selective inclusion and exclusion criteria, which excluded cardiac and neurological surgery and all patients with diseases of the central nervous system and with a previous diagnosis of delirium, or patients taking antipsychotic medication. The frequencies and distribution of genotypes found in this study population was 14%, which is somewhat lower than in previous studies (with a frequency for the *APOE4* allele in Adamis et al. [33] study of 22.4%, 23% in the study of Ely et al. [12], and 17% in the study of Abildstrom et al. [34], but it corresponds well to previous reports that denote a lesser prevalence of the *APOE4* allele in Mediterranean countries compared with northern Europe. In fact, in a Portuguese

Table 2 Patient characteristics and outcome

Variable	No delirium ($n = 147$)	Delirium ($n = 26$)	All ($n = 173$)	P value
Age in years, median (IQR)	61 (50–72)	75 (69–82)	64 (51–74)	<0.001[c]
Age group, *n* (%)				<0.001[a]
≥65 years	64 (44)	21 (81)	85 (49)	
<65 years	83 (56)	5 (19)	88 (51)	
Gender, *n* (%)				0.127[a]
Male	75 (51)	17 (65)	92 (53)	
Female	72 (49)	9 (35)	81 (47)	
ASA physical status				0.007[b]
I/II	57 (39)	3 (12)	60 (35)	
III/IV	90 (61)	23 (89)	113 (65)	
Body mass index in kg/m^2, median (IQR)	25 (23–28)	26 (23–28)	25 (23–28)	0.931[c]
Duration of anesthesia (min), median (IQR)	240 (180–300)	207 (143–300)	240 (180–300)	0.151[c]
Emergency surgery	8 (5)	6 (23)	14 (8)	0.002[a]
Type of anesthesia				0.558[b]
General/combined general locoregional	129 (88)	22 (84)	151 (87)	
Locoregional	18 (12)	4 (15)	22 (13)	
Temperature at PACU admission, median (IQR)	36.0 (34.7–36.0)	36.0 (35.0–36.0)	36.0 (34.8–36.0)	0.806[c]
Troponin I at PACU admission, median (IQR)	0.01 (0.01–0.01)	0.01 (0.01–0.05)	0.01 (0.01–0.02)	0.005[c]
Hypertension, *n* (%)	76 (52)	18 (69)	94 (54)	0.098[a]
Hyperlipidemia, *n* (%)	52 (35)	17 (65)	69 (40)	0.004[a]
High-risk surgery, *n* (%)	75 (51)	13 (50)	88 (51)	0.924[a]
Ischaemic heart disease, *n* (%)	19 (13)	12 (46)	31 (18)	<0.001[a]
Congestive heart disease, *n* (%)	37 (25)	17 (65)	54 (31)	<0.001[a]
Cerebrovascular disease, *n* (%)	21 (14)	6 (23)	27 (16)	0.255[a]
Renal insufficiency	10 (7)	4 (15)	14 (8)	0.139[b]
Insulin therapy for diabetes, *n* (%)	14 (9)	2(7)	16 (8)	0.561[b]
Total RCRI				<0.001[a]
≤2	130 (88)	15 (58)	145 (84)	
>2	17 (12)	11 (42)	28 (16)	
Katz scale, median (IQR)	0 (0–0)	0 (0–0)	0 (0–0)	0.322[c]
Dependency in I-ADL, *n* (%)	12 (8)	3 (12)	15 (9)	0.398[b]
Lawton I-ADL, median (IQR)	7 (7–7)	7 (3–7)	7 (7–7)	0.004[c]
Dependency in P-ADL, *n* (%)	25 (17)	11 (44)	36 (21)	0.004[a]

IQR interquartile range, *BMI* body mass index, *ASA* American Society of Anesthesiologists, *RCRI* Revised Cardiac Risk Index, *I-ADL* instrumental activities of daily living, *P-ADL* personal activities of daily living

[a] Pearson χ^2

[b] Fisher's exact test

[c] Mann–Whitney *U* test

study about dyslipidemia, the studied population had a frequency of 9.8% for the *APOE4* allele [35].

The most important result of this study is that there was no association between the *APOE4* allele and delirium. This lack of association was found by others [10, 33] in medical patients, but this contrasts with the report of such an association found by Leung et al. [36] in surgical patients and by van Munster [10] in a group of medical and surgical patients. The *APOE4* allele has also been associated with a longer duration of delirium in critical care medical patients [12]. The pathophysiological mechanisms of the different clinical subtypes of delirium may differ. Therefore, it could be hypothesized that there might only be an association between a particular subtype of delirium and the *APOE4* allele [12].

Other important finding of this study was that age, emergency surgery, and congestive heart failure were independent predictors for the development of postoperative delirium. Age is the most consensual predictor for delirium and has been widely reported [31, 37–40].

Table 3 Severity of disease scores, complications, and outcome

Variable	No delirium ($n = 147$)	Delirium ($n = 26$)	All ($n = 173$)	P value
SAPS II, median (P25–75)	18 (12–25)	26 (18–34)	19 (14–27)	<0.001[c]
APACHE II, median (IQR)	8 (5–10)	9 (8–11)	8 (5–11)	0.008[c]
Delirium	147	26	26 (15)	–
Acute kidney injury, *n* (%)	9 (6)	7 (27)	16 (9)	0.001[a]
Major cardiac events, *n* (%)	2 (1)	2 (8)	10 (6)	0.108[b]
PACU length of stay (h), median (IQR)	19 (15–23)	46 (19–78)	20 (15–40)	<0.001[c]
Hospital length of stay (days), median (IQR)	13 (7–23)	12 (9–27)	13 (7–25)	0.553[c]
Mortality in PACU, *n* (%)	1 (1)	0 (0)	1 (1)	–
Mortality in hospital, *n* (%)	4 (3)	9 (35)	13 (8)	<0.001[b]
Mortality at 6 months follow-up, *n* (%)	8 (5)	10 (39)	18 (10)	<0.001[a]

IQR interquartile range, *SAPS II* Simplified Acute Physiology Score, *APACHE II* Acute Physiology and Chronic Health Evaluation, *PACU* Post Anaesthesia Care Unit

[a] Pearson χ^2

[b] Fisher's exact test

[c] Mann–Whitney *U* test

Table 4 Multivariate regression analysis for predictors of delirium

Variable	Simple OR	P value	Adjusted* OR (95% CI)[a]	P value*
Age group, *n* (%)		0.001		0.004
≥65 years	5.45 (1.95–15.23)		9.30 (2.01–43.03)	
<65 years	1		1	
Emergency surgery	5.21 (1.64–16.59)	0.005	59.73 (6.72–530.48)	<0.001
ASA physical status				
I/II	1		–	
III/IV	4.86 (1.39–16.91)	0.013		
Hyperlipidemia, *n* (%)	3.45 (1.44–8.29)	0.006	–	
Ischaemic heart disease, *n* (%)	5.77 (2.33–14.34)	<0.001	–	
Congestive heart disease, *n* (%)	5.62 (2.31–13.67)	<0.001	6.21 (1.99–19.33)	0.002
RCRI, *n* (%)		<0.001		
≤2	1			
>2	5.61 (2.22–14.18)			
Previous score in Lawton scale	0.79 (0.67–0.94)	0.009		
Dependency in P-ADL, *n* (%)	3.83 (1.56–9.42)	0.003		

OR odds ratio, *CI* confidence interval, *ASA* American Society of Anesthesiologists, *RCRI* Revised Cardiac Risk Index, *P-ADL* personal activities of daily living

[a] Logistic regression analysis with stepwise forward method was used with an entry criterion of $P < 0.05$ and a removal criterion of $P > 0.1$

* Adjusted to age, emergency surgery, ASA physical status, hyperlipidemia, ischaemic heart disease, congestive heart disease, RCRI, previous Lawton scale and dependency in P-ADL

Ansaloni et al. [41] found that emergency surgery was significantly associated with the onset of postoperative delirium in a case–control study in surgical patients, but in that study, emergency was not independently associated with higher risk of postoperative delirium, as occurred in our study. In emergent patients, some interventions highly effective in an elective situation, for example, nonpharmacological interventions such as counselling for family and patient and adjustment of environmental conditions such as light and temperature may be lacking because they are not always easily adaptable to an emergent setting.

To our knowledge, there are no references in the literature about the relationship of congestive heart disease and postoperative delirium. Inouye and Charpentier [30] described predisposing and precipitating factors for postoperative delirium, noting that the risk of developing delirium increases with each additional risk factor present and predisposing factors, such as age or comorbidities.

Table 5 Patient characteristics and outcome

Variable	With *APOE4* ($n = 24$)	Without *APOE4* ($n = 149$)	*P* values
Age in years, median (IQR)	62 (50–71)	65 (51–74)	0.888[c]
Age group, *n* (%)			0.430[a]
≥65 years	10 (58)	75 (50)	
<65 years	14 (42)	74 (50)	
Gender, *n* (%)			0.223[a]
Male	10 (42)	82 (55)	
Female	14 (58)	67 (45)	
ASA physical status			0.216[a]
I/II	11 (46)	49 (33)	
III/IV	13 (54)	100 (67)	
Body mass index in kg/m^2, median (IQR)	26 (24–29)	25 (23–28)	0.687[c]
Duration of anaesthesia (min), median (IQR)	244 (169–345)	235 (180–300)	0.180[c]
Emergency surgery	1 (4)	13 (9)	0.392[b]
Type of anesthesia			0.124[b]
General/combined general locoregional	24 (100)	127 (85)	
Locoregional	0 (0)	22 (15)	
Temperature at PACU admission, median (IQR)	36.0 (34.7–36.0)	36.0 (34.9–36.0)	0.985[c]
Troponin I at PACU admission, median (IQR)	0.01 (0.01–0.03)	0.01 (0.01–0.02)	0.710[c]
Hypertension, *n* (%)	9 (38)	85 (57)	0.074[a]
Hyperlipidemia, *n* (%)	8 (33)	61 (41)	0.480[a]
High-risk surgery, *n* (%)	10 (42)	78 (52)	0.331[a]
Ischemic heart disease, *n* (%)	3 (13)	28 (19)	0.337[b]
Congestive heart disease, *n* (%)	6 (25)	48 (32)	0.479[a]
Cerebrovascular disease, *n* (%)	2 (8)	25 (17)	0.233[b]
Renal insufficiency	0 (0)	14 (9)	0.117[b]
Insulin therapy for diabetes, *n* (%)	1 (4)	12 (8)	0.436[b]
Total RCRI			0.429[a]
≤2	21 (88)	124 (83)	
>2	3 (12)	25 (17)	
Katz scale, median (IQR)	0 (0–0)	0 (0–3)	0.627[c]
Dependency in I-ADL, *n* (%)	2 (8)	13 (9)	0.654[b]
Lawton I-ADL, median (IQR)	7 (7–7)	3 (1–5)	0.674[c]
Dependency in P-ADL, *n* (%)	4 (17)	32 (22)	0.403[b]
SAPS II, median (P25–75)	20 (12–26)	18 (14–27)	0.884[c]
APACHE II, median (IQR)	7 (5–11)	8 (5–11)	0.797[c]
Delirium	1 (4)	25 (17)	0.088[b]
Acute kidney injury	2 (8)	14 (9)	0.612[b]
Acute cardiac events	0 (0)	4 (3)	0.547[b]
PACU length of stay (h), median (IQR)	20 (15–41)	20 (12–26)	0.215[c]
Hospital length of stay (days), median (IQR)	12 (8–28)	13 (7–24)	0.202[c]
Mortality in PACU, *n* (%)	1 (1)	0 (0)	–
Mortality in hospital, *n* (%)	0 (0)	13 (9)	0.132[b]
Mortality at 6 months follow-up	2 (8)	16 (11)	0.530[b]

IQR interquartile range, *APOE4* apolipoprotein E epsilon 4 allele, *ASA* American Society of Anesthesiologists, *RCRI* Revised Cardiac Risk Index, *I-ADL* instrumental activities of daily living, *P-ADL* personal activities of daily living, *SAPS II* Simplified Acute Physiology Score, *APACHE II* Acute Physiology and Chronic Health Evaluation, *PACU* Post Anaesthesia Care Unit

[a] Pearson χ^2

[b] Fisher's exact test

[c] Mann–Whitney *U* test

Indeed, in our study, patients who developed delirium were also more severally ill, and congestive heart failure was an important comorbidity [31, 37–40]. In older patients, interconnected precipitating factors may trigger delirium through a series of additional factors more prone to be present in these patients (greater dependency for ADL, prescribed medication reinitiated or increased, pain, constipation, or even loss of senses such as hearing and vision).

Although others have similar results indicating the association of delirium with poor outcome [1, 4, 12], our results indicate that patients with delirium were not only more severely ill but stayed longer in the PACU and had higher mortality rates, even when considering mortality rates at 6 months' follow-up. Patients with delirium had mortality rates ten times higher at hospital discharge and almost eight times higher at 6 months' follow-up, and their PACU LOS was more than two times higher. Other authors [10, 36] found that patients with delirium had more frequently functional impairment, and our results are in agreement, indicating a higher degree of dependency in patients with postoperative delirium and lower scores in Lawton P-ADL scale.

Another important result from our study indicates that patients who develop postoperative delirium more frequently have AKI. As far as we know, this is the first study to evaluate the connection between AKI and the development of postoperative delirium. This condition may act as a precipitating factor in vulnerable patients and may imply that a present complication after surgery may contribute to delirium or that delirium may be a presenting factor of AKI. We found no differences in the incidence of delirium according to anesthesia type, although this has been reported for elderly patients, in particular, undergoing general anesthesia [42], Bryson et al. [43] concluded in their evidence-based clinical update that the available randomized controlled trials suggest there is no significant difference in the incidence of delirium when general anesthesia and regional anesthesia are compared.

This study has several limitations that must be addressed. We excluded patients with previous neurological disorders and patients submitted to cardiac surgery, which may have lowered the incidence of postoperative delirium. Patients with previous neurological disorders that may predispose or manifest in the postoperative period as delirium were excluded because of the possibility of false positive diagnosis. Patients after cardiac surgery were also excluded, because these types of surgery have been associated with perioperative biochemical disturbances that influence cerebral activity and some variables that seem to have a role in the etiology of delirium, factors that could lead to a higher postoperative delirium occurrence. Also, our sample was not homogenous, as we included adult patients with a wide range of ages and patients submitted to a variety of major surgeries. Anesthetic management in our patients was not standardized: there was no anesthetic protocol to follow, and the depth of anesthesia was not measured, which may be considered a limitation of the study. Also, we focused on measuring delirium in the early postoperative period. As a result, incidents of later-onset delirium may have been missed. The frequency distribution of *APOE4* was lower than expected, and the sample may have been small enough to denote statistically significant conclusions. Larger studies in different homogeneous patient populations are needed to evaluate the potential importance of genetic influences as one of the several etiologic factors for the development of postoperative delirium.

Conclusions

In conclusion, we could not show a significant association between *APOE* genotype and postoperative delirium after major surgery; however, age, emergency surgery, and congestive heart failure were considered independent risk factors. Delirium had a significant impact on length of PACU stay and mortality rate.

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