



Articles

Assessment of indirect effects of apolipoprotein Eε4 carrier status on postoperative delirium incidence in cardiac surgery – A preplanned secondary analysis of a prospective cohort study

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Delirium Communications

Background

Although postoperative delirium is a frequent complication, its pathophysiological mechanisms have not been completely elucidated yet. Recent studies suggested indirect influences of apolipoprotein Eε4 (APOEε4) allele, a genetic risk factor of Alzheimer's disease, on the association between postoperative delirium and some known risk factors.

Objectives

This preplanned secondary analysis ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03706989) NCT03706989) aimed to determine whether APOEε4 carrier status played an indirect role on postoperative delirium incidence related to (1) preoperative cognitive impairment and to (2) postoperative inflammation in cardiac surgery.

Methods

220 adult patients undergoing elective cardiac surgery were included in the study. Preoperative cognitive assessment was performed the day before surgery using both a battery of five neuropsychological tests and the Mini-Mental State Examination. Postoperative inflammation was evaluated by C-reactive protein (CRP) concentrations in blood. Patients were screened for postoperative delirium from the Intensive Care Unit until discharge from the hospital using CAM-ICU (3 times a day in the ICU), CAM (2 times a day at the ward) and a chart review. Comparisons between groups were performed using a χ^2 test for dichotomous variables and a Student t-test for continuous variables. Association between the studied exposure (preoperative cognition or postoperative systemic inflammation) and the incidence of postoperative delirium, as well as their respective interactions with APOEε4 carrier status, were assessed using multivariable logistic regression models.

Results

Among 220 cardiac surgery patients, 65 (29.5%) developed delirium. Fifty-three patients (24%) carried at least one allele ε4. Multivariable logistic regression models showed that (1) interactions between APOEε4 carrier status and preoperative cognitive status or between APOEε4 carrier status and postoperative CRP concentrations were negligible, and (2) extensive preoperative cognitive testing remained a key predictor of postoperative delirium.

Discussion

APOEε4 carrier status did not modify the effect of preoperative cognitive impairment or the effect of higher postoperative systemic inflammation on postoperative delirium occurrence in our clinical series.

INTRODUCTION

Alzheimer's disease (AD) is one of the most prevalent forms of dementia, with an incidence of up to 40% in older adults.¹ Postoperative delirium shares epidemiologic characteristics with AD. Indeed, pre-existing cognitive impairment is a leading predisposing risk factor for delirium²; and AD patients who developed postoperative delirium have a higher risk of cognitive decline after surgery.³

The hypothesis of a genetic predisposition for postoperative neurocognitive disorders arose after apolipoprotein Eε4 (APOEε4) allele, a strong genetic risk factor for familial and sporadic late onset AD,⁴ had been shown to play a role in recovery from acute brain injury. Whereas APOE demonstrated potential neurotrophic, immunomodulatory and antioxidant effects,⁵⁻⁸ it also has been demonstrated that the presence of the ε4 allele determined a greater incidence of mortality and poorer functional recovery among subjects who had suffered from acute ischemic insults.^{9,10}

However, studies which investigated a direct association between the presence of APOEε4 allele and the incidence of postoperative neurocognitive disorders have shown conflicting results,¹¹⁻²¹ with the majority of latest studies in favor of a lack of association.^{12-14,16-21}

Recently, studies on gene-protein interactions suggested a more indirect genetic influence on the occurrence of postoperative delirium.^{22,23} For instance, it has been shown that patients who carried at least one allele ε4 and who developed higher postoperative C-reactive protein (CRP) concentrations had an increased risk of postoperative delirium, whereas such an association between CRP concentrations and delirium was not found in APOEε4 non-carriers.²³ Consequently, APOEε4 allele might be an indicator of brain vulnerability, which indirectly modifies the relationship between postoperative delirium and some of its key predisposing or precipitating risk factors.

In this secondary analysis, we hypothesized that APOEε4 carrying cardiac surgery patients who had abnormal scores on preoperative cognitive assessment (predisposing risk factor of delirium) were at higher risk of postoperative delirium. We also tested the indirect influence of APOE genotype on the relationship between higher postoperative systemic inflammation (precipitating risk factor of delirium), as measured by peak postoperative CRP concentration, and the occurrence of postoperative delirium.

METHODS

This preplanned secondary study is part of a monocentric prospective observational project in which the primary aim was to assess the association between lower intraoperative frontal α-band power of the electroencephalogram (EEG) and the occurrence of postoperative delirium.²⁴ This project was approved on September 2018 by Comité d'Ethique Hospitalo-Facultaire of Cliniques universitaires Saint-Luc (2018/20SEP/350, Brussels, Belgium – chairman Pr. J-M Maloteaux) and registered in [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03706989) (NCT03706989) before the start of the trial. Written informed consent was obtained from all patients, according

to the Declaration of Helsinki. The project included 220 adult patients who underwent a first elective cardiac surgery by sternotomy under cardiopulmonary bypass. Data from this cohort have been reported previously, including the study flow diagram (see Supplementary Material for details).²⁴ Particularly relevant for the current analyses, patients suffering from psychiatric disorders or presenting with preoperative delirium were excluded from the trial. Surgical exclusion criteria were emergencies, endocarditis, ventricular assist devices, heart transplantations, minimally invasive and robotic surgeries. Patients were screened for postoperative delirium by trained nurses using the Confusion Assessment Method for Intensive Care Unit three times a day in the Intensive Care Unit, then using the Confusion Assessment Method twice daily at the ward until hospital discharge. Additionally, the medical chart was systematically checked by the research team for any notifications suggesting an episode of delirium.

PREOPERATIVE NEUROCOGNITIVE EVALUATION

Enrolled patients were evaluated by two types of preoperative cognitive assessment. First, a succinct global cognitive screening was assessed by the Mini-Mental Examination (MMSE). Patients were afterwards submitted to a battery of five neuropsychological tests chosen based on the previous work of McDonagh *et al.*¹⁷ and covering more exhaustively different cognitive domains: the 16-item Free and Cued Selective Reminding Test, the Modified Visual Reproduction Test from the Wechsler Memory Scale, the Digit Span Test, the Trail Making Test (time part B minus time part A) and the Digit Symbol Test. To score cognitive status using this battery of test, a z-score was ultimately calculated after averaging sample-specific z-scores from each test. Two members of the research team were trained by neuropsychologists from our Department of Neurology to conduct this evaluation. All preoperative cognitive assessments took place the day before surgery.

APOLIPOPROTEIN E GENOTYPING

Whole blood was performed for APOE genotyping. Blood was collected in 3.4ml EDTA tubes (S-Monovette®, Sarstedt B.V., Nümbrecht, Germany) and stored at -4°C for a maximum of 48 hours before analysis by "Institut de Pathologie and Génétique" (Gosselies, Belgium). APOE haplotype status, which depends on the genotypes of 2 single-nucleotide polymorphisms, was determined by PCR amplification, followed by Sanger Sequencing. Patients were considered APOEε4(+) when they carried at least 1 allele ε4.

POSTOPERATIVE CRP MEASUREMENTS

Postoperative CRP concentrations in serum were monitored daily until day 3, then according to individual postoperative clinical evolution. Blood samples for CRP measurements were collected on heparin tubes (S-Monovette®, Sarstedt B.V., Nümbrecht, Germany) and directly analyzed by our Biochemical Laboratory (Brussels, Belgium). Measurements were performed in singlicate. Intra-assay coefficient of

variation was 2.2% for a CRP concentration in serum of 3.7 mg/l. The lower limit of detection was 0.3 mg/l (2.9 nmol/l). There were 1 missing analysis on postoperative day 1, 3 on postoperative day 2 and 16 on postoperative day 3. For each patient, the peak postoperative CRP concentration was recorded.

STATISTICAL ANALYSES

Categorical data are presented as numbers and percentages. Continuous variables are presented as means $\pm$ standard deviations (SD) or medians [range]. Comparisons between groups were performed using a χ^2 test for dichotomous variables and a Student t-test for continuous variables.

A direct effect of APOEε4 carrier status on postoperative delirium incidence was assessed by a univariable logistic regression analysis.

Association between the exposure (preoperative cognitive status and peak of postoperative CRP concentrations) and the incidence of postoperative delirium, as well as their respective interactions with APOEε4 carrier status on the incidence of postoperative delirium, were assessed using multivariable logistic regression models. For analyses regarding preoperative cognitive status, two different multivariable logistic regression models were performed including either MMSE or the cognitive z-score. Covariates were selected on the basis of clinical relevance, results of univariable analyses and specific study hypotheses. *Model 1* is a model including the effect of APOEε4 carrier status adjusted for age, EuroSCORE II (European System for Cardiac Operative Risk Evaluation) score (score that estimates the risk of in-hospital mortality after cardiac surgery based on patient's cardiovascular comorbidities and surgical specificities), sex, exposure of interest (cognitive status evaluated by MMSE or cognitive z-score, and CRP), as well as the interactions of these covariates with APOEε4 carrier status. *Model 2* is a model of the effect of APOEε4 carrier status adjusted for the abovementioned covariates but without considering interactions. *Model 3* is a model of the effect of APOEε4 carrier status after removing nonsignificant covariates. Because models were hierarchical, comparisons between models were assessed using both the Likelihood Ratio test (LRT) and the Akaike Information Criterion (AIC) that has to be a minimum. A *P*-value <0.05 was considered statistically significant. All statistics were performed using IBM SPSS Statistics version 27.

RESULTS

The distribution of APOE genotypes ([Fig. 1](#)) was consistent with the Hardy-Weinberg equilibrium ($\chi^2 = 2.52$; *df* = 3; *P* = 0.471). Among the 220 patients, 138 (63%) expressed an ε3ε3 haplotype. Fifty-three patients (24% of the cohort) carried at least one ε4 allele. Sixty-five patients (29.5% of the cohort) developed postoperative delirium, among whom 14 were APOEε4 carriers.

Demographics and perioperative clinical data of our cohort are reported in [Table 1](#). A majority of the patients were

males (81.8%) and the median age was 69 years old (range from 18 to 87 years old). Variables detailed in [Table 1](#) were similar among APOEε4 carriers and non-carriers.

Particularly, the presence of the ε4 allele was not significantly different among patients with and without postoperative delirium: 39/155 patients (25.2%) in the “non-delirium” group vs 14/65 patients (21.5%) in the “delirium” group (*P* = 0.566).

The absence of a direct effect of APOEε4 carrier status on postoperative delirium incidence was confirmed by a univariable logistic regression analysis (Odds Ratio [95% CI], 0.82 [0.41 – 1.63]; *P* = 0.567).

[Table 2](#) reports the multivariable logistic regression models assessing the effects of relevant covariates, including MMSE, APOEε4 carrier status and their interactions, on postoperative delirium incidence. The AIC was minimum with *Model 3*, using a LRT for comparing *Model 3* to *Model 2*, $\chi^2 = 3.54$; *df* = 2; *P* = 0.170.

[Table 3](#) reports the multivariable logistic regression models assessing the effects of relevant covariates, including preoperative cognitive z-score, APOEε4 carrier status and their interactions, on postoperative delirium incidence. In this case, the AIC was minimum with *Model 2*, using a LRT for comparing *Model 2* to *Model 1*, $\chi^2 = 5.14$; *df* = 4; *P* = 0.273. *Model 2* was also significantly different from *Model 3*, which only included age, EuroSCORE II and APOEε4 carrier status (LRT comparing *Model 3* to *Model 2* $\chi^2 = 10.13$; *df* = 2; *P* = 0.006).

Peak CRP concentrations were mainly reached either on postoperative day 2 (46.3%) or on day 3 (52.3%). The median of peak postoperative CRP concentration for the entire cohort was 213.8 mg/l.

[Table 4](#) reports the multivariable logistic regression models assessing the effects of relevant covariates, including peak of postoperative CRP, APOEε4 carrier status and their interactions, on postoperative delirium incidence. The AIC was minimum with *Model 3*, and using a LRT for comparing *Model 3* to *Model 2*, $\chi^2 = 1.67$; *df* = 2; *P* = 0.434.

Results of our models indicated that (1) selected interactions with APOEε4 carrier status were negligible for both exposures (cognitive status and CRP), meaning that APOEε4 carrier status did not modify the effect of other covariates on postoperative delirium occurrence, (2) a model including age and EuroSCORE II scores was as good as models including risk factors such as baseline cognition assessed with MMSE or postoperative inflammation, and (3) preoperative cognitive status evaluated using a complete battery of neuropsychological tests brings a significant added value compared to a model including only age and EuroSCORE II when predicting delirium incidence after cardiac surgery.

DISCUSSION

This preplanned secondary study confirms recent observations of an absence of direct influence of APOE genotype on the occurrence of postoperative delirium after cardiac surgery.^{17,23} It highlights that although APOEε4 allele is a genetic risk factor for AD, postoperative neurocognitive

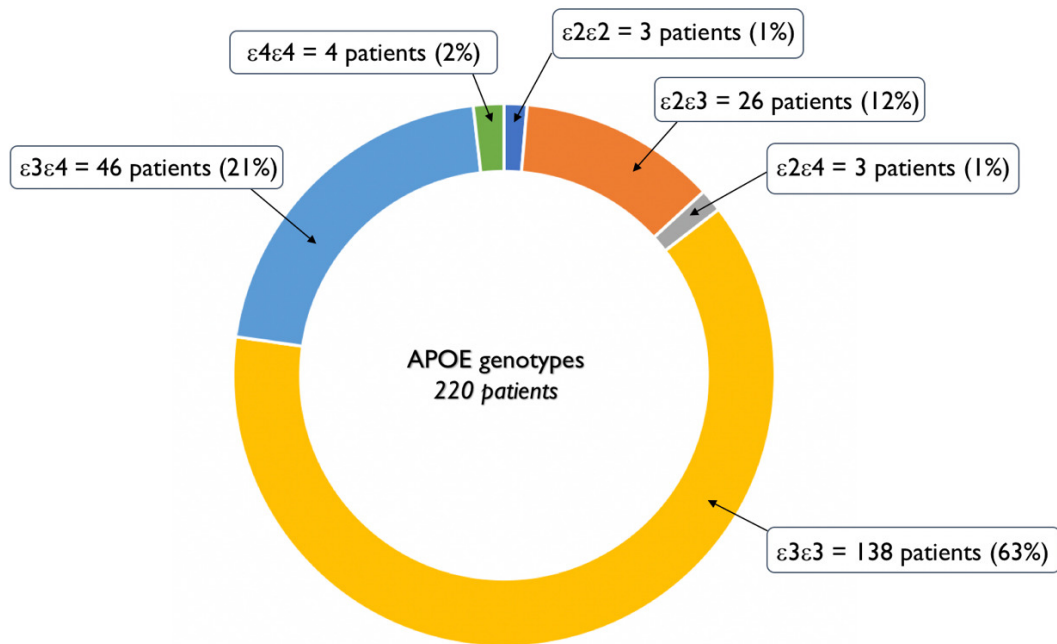


Figure 1. Distribution of APOE genotypes among the clinical series

disorders and AD remain two distinct conditions, despite some evidence of a potential relationship.^{2,3}

More importantly, we were not able to validate our a priori hypothesis, as we did not find any indirect effect of APOEε4 carrier status on postoperative delirium incidence among patients with poorer preoperative cognitive results or among those who developed higher postoperative systemic inflammation. First, our results might indicate that the combination of APOEε4 carrier status and abnormal preoperative cognitive results does not exert a synergistic effect on postoperative delirium incidence. Nonetheless, this finding needs to be interpreted cautiously. To our knowledge, no previous study assessed the indirect impact of a genetic predisposition to AD on the association between cognitive impairment and postoperative delirium. Moreover, our results also highlighted that multivariable logistic regression models to predict postoperative delirium including results from a succinct global cognitive test or from a standardized battery of neuropsychological tests revealed completely different efficiency. Indeed, while a model including MMSE was of no added value to a model including age and EuroSCORE II, a model including a more exhaustive cognitive assessment might be a promising way to help identifying patients at risk of delirium after surgery. This finding is in accordance with the current lack of recommendation as which screening test should be used to assess preoperative cognitive status.²⁵⁻²⁷ The main reason is that the predictive power of easier screening tests remains to be evaluated, especially in comparison with a complete battery of neuropsychological tests. Otherwise, we did not evaluate the relationship between APOEε4 carrier status and deficits in specific cognitive domains previously associated with postoperative delirium, such as deficits in executive and language functions.²⁸ Hence, studies are needed

to further investigate whether APOE genotype modifies the effect of domain-specific cognitive impairment on the incidence of postoperative neurocognitive disorders, in order to ease preoperative cognitive evaluation in the future.

Additionally, our results also failed to demonstrate any significant association between higher postoperative inflammation and delirium incidence in APOEε4 carriers. In this regard, our findings differ from the work of Vasunilashorn *et al.*,²³ in which the authors observed a strong relationship between high CRP concentration at postoperative day 2 and delirium incidence, severity and duration among APOEε4 carriers after non-cardiac surgery. A first important reason could arise from our smaller population sample size, including 220 patients compared to 553 subjects in the study performed by Vasunilashorn. Indeed, whereas sample size calculation is of utmost importance in genetic studies,²⁹ our sample size calculation was based on the primary objective of the study, which was the evaluation of intraoperative EEG spectral analysis component as potential predictive marker of postoperative delirium in cardiac surgery.²⁴ Another plausible explanation could be the difference in the studied population. We included adult patients >18 years old, whereas the other study focused on patients >70 years old. We chose to enroll adult cardiac surgery patients of any age because, in our clinical experience, patients may present episodes of delirium after cardiac surgery at any age, especially in the presence of lower preoperative cognitive scores. A third reason distinguishing our results from those of Vasunilashorn *et al.* could be the difference in the definition of postoperative CRP. We looked at peak postoperative CRP instead of arbitrarily focusing on concentrations measured on one postoperative day specifically. Indeed, in our cohort, we observed that the maximum

Table 1. Demographics and perioperative clinical data of APOEε4 carrier and non-carrier patients

		Entire cohort (n = 220)	APOEε4 (-) (n = 167)	APOEε4 (+) (n = 53)	P
Pre-operative data					
Age, years	Mean (SD)	67 (11)	68 (11)	65 (12)	0.167 ^a
	Median	69	70	64	
	Range	18 - 87	18 - 87	31 - 86	
Sex, male		180 (81.8)	134 (80.2)	46 (86.8)	0.281 ^b
MMSE < 28/30		74 (33.6)	59 (35.3)	15 (28.3)	0.345 ^b
Low educational level (< 9 years)		59 (n=202) (26.8)	46 (n=153) (30.1)	13 (n=49) (26.5)	0.636 ^b
EuroSCORE II, %	Mean (SD)	2.23 (1.76)	2.31 (1.78)	1.99 (1.70)	0.228 ^a
	Median	1.69	1.85	1.32	
	Range	0.50 - 9.73	0.50 - 9.73	0.50 - 8.52	
Intra-operative data					
Type of surgery					0.250 ^b
Isolated CABG		100 (45.5)	79 (47.3)	21 (39.6)	
Single non-CABG		45 (20.5)	34 (20.4)	11 (20.8)	
2 interventions		50 (22.7)	33 (19.8)	17 (32.1)	
≥ 3 interventions		25 (11.4)	21 (12.6)	4 (7.5)	
Surgical time, min	Mean (SD)	230 (58)	228 (59)	234 (56)	0.515 ^a
	Median	227	225	228	
	Range	105 - 444	105 - 444	120 - 355	
CPB time, min	Mean (SD)	103 (36)	102 (36)	106 (36)	0.463 ^a
	Median	98	97	105	
	Range	36 - 278	36 - 278	43 - 231	
Postoperative data					
Mechanical ventilation time, h	Mean (SD)	8 (5)	8 (5)	7 (4)	0.073 ^a
	Median	7	7	7	
	Range	3 - 40	3 - 40	3 - 21	
Postoperative delirium		65 (29.5)	51 (30.5)	14 (26.4)	0.566 ^b
Peak C-reactive protein, mg/l	Mean (SD)	216.6 (72.0)	217.1 (71.4)	214.9 (74.5)	0.846 ^a
	Median	213.7	211.8	217.9	
	Range	30.5 - 393.4	47.0 - 393.4	30.5 - 385.0	
Reintervention for bleeding		12 (5.5)	10 (6.0)	2 (3.8)	0.586 ^b
ICU length of stay, days	Mean (SD)	3 (2)	3 (2)	3 (2)	0.724 ^a
	Median	2	2	2	
	Range	1 - 21	1 - 21	1 - 9	
Hospital length of stay, days	Mean (SD)	9 (4)	9 (3)	9 (4)	0.957 ^a
	Median	8	8	8	
	Range	5 - 29	6 - 25	5 - 29	

Continuous variables are expressed as means ± SD, medians and ranges. Categorical variables are expressed as numbers (percentages). Number of patients with available data are mentioned between brackets. * $P < 0.05$. P-values refer to group comparison by: ^aStudent-t test; ^bChi-square test. APOEε4(+) defined as ε2ε4, ε3ε4 or ε4ε4. ^cLow educational level (< 9

years)* corresponds to patients who did not finish regular school in our country (Belgium). Abbreviations: APOE: Apolipoprotein E; CABG: Coronary Artery Bypass Grafting; CPB: Cardiopulmonary Bypass; EuroSCORE: European System for Cardiac Operative Risk Evaluation; Hb: Hemoglobin; ICU: Intensive Care Unit; MMSE: Mini-Mental State Examination

Table 2. Odds Ratio for postoperative delirium incidence in the clinical series, using multivariable logistic regression. (Exposures = APOEε4 carrier status and MMSE)

Variables	Model 1	Model 2	Model 3
	Odds ratio (95% CI)		
Age, deciles	1.28 (0.89 – 1.85)	1.34 (0.97 – 1.86)	1.46 (1.07 – 1.99)
EuroSCORE II, %	1.22 (1.00 – 1.48)	1.27 (1.06 – 1.52)	1.27 (1.06 – 1.51)
APOEε4 (+)	7.46 (0.00 – 2.44·10 ⁶)	0.96 (0.46 – 2.01)	0.93 (0.44 – 1.93)
Sex, male	0.97 (0.40 – 2.31)	1.27 (0.56 – 2.88)	-
MMSE, /30	0.90 (0.78 – 1.04)	0.87 (0.76 – 1.01)	-
Interactions			
Age x APOEε4 (+)	1.16 (0.51 – 2.65)	-	-
EuroSCORE II x APOEε4 (+)	1.21 (0.71 – 2.06)	-	-
Sex x APOEε4 (+)	6.59 (0.42 – 104.17)	-	-
MMSE x APOEε4 (+)	0.83 (0.49 – 1.41)	-	-
AIC	259.66	255.21	254.75
LRT χ^2 (1 vs 2, 2 vs 3)		3.55	3.54
df		4	2
P-value		0.470	0.170

Model 1 is an adjusted model including APOEε4 carrier status with additional covariates of age, EuroSCORE II, sex, MMSE and interactions of covariates with APOEε4 carrier status. *Model 2* includes APOEε4 carrier status with additional covariates of age, EuroSCORE II, sex and MMSE. *Model 3* includes APOEε4 carrier status with additional covariates of age and EuroSCORE II. Bold characters indicate $P < 0.05$. Abbreviations: AIC: Akaike Information Criterion; APOE: Apolipoprotein; EuroSCORE: European System for Cardiac Operative Risk Evaluation; LRT: Likelihood Ratio test; MMSE: Mini-Mental State Examination

Table 3. Odds Ratio for postoperative delirium incidence in the clinical series, using multivariable logistic regression. (Exposures = APOEε4 carrier status and cognitive z-score)

Variables	Model 1	Model 2	Model 3
	Odds ratio (95% CI)		
Age, deciles	1.31 (0.76 – 1.68)	1.09 (0.76 – 1.56)	1.46 (1.07 – 1.99)
EuroSCORE II, %	1.18 (0.97 – 1.43)	1.21 (1.01 – 1.45)	1.27 (1.06 – 1.51)
APOEε4 (+)	0.33 (0.00 – 400.55)	0.95 (0.44 – 2.04)	0.93 (0.44 – 1.93)
Sex, male	0.91 (0.39 – 2.13)	1.20 (0.44 – 2.04)	-
Cognitive Z-score	0.64 (0.41 – 0.99)	0.54 (0.36 – 0.80)	-
Interactions			
Age x APOEε4 (+)	0.85 (0.33 – 2.20)	-	-
EuroSCORE II x APOEε4 (+)	1.12 (0.59 – 2.13)	-	-
Sex x APOEε4 (+)	8.56 – 0.47 (155.99)	-	-
Cognitive Z-score x APOEε4 (+)	0.43 (0.14 – 1.29)	-	-
AIC	251.48	248.62	254.75
LRT χ^2 (1 vs 2, 2 vs 3)		5.14	10.13
df		4	2
P-value		0.273	0.006

Model 1 is an adjusted model including APOEε4 carrier status with additional covariates of age, EuroSCORE II, sex, cognitive z-score and interactions of covariates with APOEε4 carrier status. *Model 2* includes APOEε4 carrier status with additional covariates of age, EuroSCORE II, sex and cognitive z-score. *Model 3* includes APOEε4 carrier status with additional covariates of age and EuroSCORE II. Bold characters indicate $P < 0.05$. Abbreviations: AIC: Akaike Information Criterion; APOE: Apolipoprotein; EuroSCORE: European System for Cardiac Operative Risk Evaluation; LRT: Likelihood Ratio test.

Table 4. Odds Ratio for postoperative delirium incidence in the clinical series, using multiple logistic regression. (Exposures = APOEε4 carrier status and peak of postoperative CRP)

Variables	Model 1	Model 2	Model 3
Odds ratio (95% CI)			
Age, deciles	1.40 (0.98 – 1.99)	1.48 (1.08 – 2.03)	1.46 (1.07 – 1.99)
EuroSCORE II, %	1.18 (0.97 – 1.43)	1.24 (1.03 – 1.48)	1.27 (1.06 – 1.51)
APOEε4 (+)	0.04 (0.00 – 41.19)	0.93 (0.45 – 1.95)	0.93 (0.44 – 1.93)
Sex, male	0.78 (0.34 – 1.81)	1.00 (0.45 – 2.20)	-
Max. CRP, mg/l	1.00 (1.00 – 1.01)	1.00 (1.00 – 1.01)	-
Interactions			
Age x APOEε4 (+)	1.24 (0.56 – 2.75)	-	-
EuroSCORE II x APOEε4 (+)	1.29 (0.76 – 2.19)	-	-
Sex x APOEε4 (+)	6.62 (0.43 – 102.97)	-	-
CRP x APOEε4 (+)	1.00 (0.99 – 1.01)	-	-
AIC	261.38	257.08	254.75
LRT χ^2 (1 vs 2, 2 vs 3)		3.7	1.67
df		4	2
P-value		0.448	0.434

Model 1 is an adjusted model including APOEε4 carrier status with additional covariates of age, EuroSCORE II, sex, peak of postoperative CRP concentrations and interactions of covariates with APOEε4 carrier status. *Model 2* includes APOEε4 carrier status with additional covariates of age, EuroSCORE II, sex and peak of postoperative CRP concentrations. *Model 3* includes APOEε4 carrier status with additional covariates of age and EuroSCORE II. Bold characters indicate $P < 0.05$. Abbreviations: AIC: Akaike Information Criterion; APOE: Apolipoprotein; CRP: C-Reactive Protein; EuroSCORE: European System for Cardiac Operative Risk Evaluation; LRT: Likelihood Ratio test.

postoperative CRP concentration occurred mostly either on postoperative day 2 or day 3.

In conclusion, we found an absence of specific indirect effect of APOE genotype on the incidence of postoperative delirium in cardiac surgery, as interactions between APOEε4 carrier status and predisposing (preoperative cognitive status) or precipitating (peak of postoperative CRP concentrations) risk factors of delirium were negligible in our clinical series. Nonetheless, further dedicated studies with appropriate sample size are required to properly investigate (1) a potential synergistic effect of a genetic predisposition to AD and preoperative deficits in specific cognitive domains and (2) the “gene-protein” interaction hypothesis as a pathophysiological mechanism of postoperative neurocognitive disorders.

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AUTHORS CONTRIBUTIONS

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Céline Khalifa, Bernard Grisart, Adrian Ivanoiu and Mona Momeni. The first draft of the manuscript was written by Céline Khalifa and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY STATEMENT

The data supporting the findings of this study are available within the article.

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COMPETING INTERESTS

The authors have no competing interests to declare that are relevant to the content of this article.

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