

## Analysis of Genetic predispositions for Cognitive decline after Cardiac Surgery

Shafqat Hussain<sup>1</sup>, Rashid Ali Malik<sup>2</sup>, Muhammad Yasir Khan<sup>3</sup>

### ABSTRACT

**Objective:** To analyze the effect of Apo lipoprotein E-ε4 allele mediated genetic predispositions on cognitive impairment in patients with post-cardiac procedures.

**Study Design:** A cohort observational study design.

**Place and Duration:** From 1<sup>st</sup> Aug 2020 to 1<sup>st</sup> Jan 2021 at Cardiac Surgery Department of Ch. Pervaiz Elahi Institute of Cardiology, Multan.

**Methodology:** Patients undergoing coronary bypass surgery were evaluated for Apo lipoprotein E-ε4 allele based post-operative cognitive dysfunction. The major outcomes of the study were analyzed on the basis of cognitive performance at two levels mainly at pre-coronary surgery and post-coronary surgery after an interval of 07 weeks.

**Results:** The genotyping of the patients (n=45) revealed the presence of the APOE ε4 allele in 73% and absence in 27% of the total patients respectively. Results show that no statistically significant difference was observed in the mean values of the descriptive variables or the baseline psychological measurement scores (means) for both the presence and absence of Apo lipoprotein E-ε4 respectively. The multivariable logistic regression analysis revealed no significant relationship with age. However, a significant relationship was observed between the presence of APOE-ε4 allele and cognitive dysfunction in patients who underwent coronary surgery after an interval of 7 weeks.

**Conclusion:** A significant correlation is observed between the presence of APOE-ε4 allele and cognitive dysfunction in patients who underwent coronary surgery after an interval of 7 weeks. Moreover, no significant relationship was observed with age.

**Keywords:** Cardiac surgery, Apo lipoprotein E (APOE), E-ε4 allele, Cognitive decline, Genetic predispositions, Postoperative cognitive dysfunction (POCD)

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### INTRODUCTION

The neurocognitive decline subsequent to surgery is often referred to as the postoperative cognitive dysfunction (POCD)<sup>1</sup>.

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Most prominently, it is frequently reported that a cognitive decline usually occurs and persists after cardiac surgery in a considerable number of patient<sup>2,3</sup>. However, in terms of post-surgery effects, little variance in cognitive decline has been reported for various perioperative factors (i.e. micro emboli or aspects of operation) in combination with features such as age<sup>2,3</sup>. This speculates the need to elucidate yet other unidentified characteristics that might have a pivotal role in contributing to the observable changes. As a patient associated factor, an explanatory role has been proposed for the Apo lipoprotein E (APOE) gene (with allele's ε2, ε3, and ε4)<sup>4-6</sup>.

The Apo lipoprotein E (APOE) was initially identified to be crucial for lipoprotein metabolism and cardiovascular diseases but recently it is implicated to be involved in the Alzheimer's disease and cognitive function<sup>5</sup>. Recent literature supports an increased risk of Alzheimer's disease, and cognitive impairment with the presence of APOE ε4 allele<sup>7</sup>. However, various studies based on cardiac and non-cardiac surgeries have reported a likely relationship between APOE ε4 allele and POCD<sup>5,8,9</sup>. Most prominently, for cardiac patients undergoing surgery a statistically significant relationship has been observed between the POCD (one week postoperative) and the presence of APOE ε4 alleles<sup>10-13</sup>. This indicates that the presence of APOE ε4 allele might increase the risks of POCD<sup>14</sup>.

Therefore, the exploration of the role of APOE  $\epsilon$ 4 allele and its association with different biological processes is a major focus of current research, mainly owing to its association with cognitive impairment in the patients with post-cardiac operations and other surgeries. However, literature also reports increasing evidence that the cerebrovascular risk factors are amongst the patient-related features that might also play a crucial role in the early and late postoperative cognitive impairment<sup>15</sup>. The adverse neurologic outcomes and cognitive dysfunctional ties have emerged as a major concern for patients undergoing cardiac surgeries. However, the presence of minor cognitive defects prior to surgery can also lead to increased risks of cerebrovascular disease<sup>16</sup>. Therefore, there is a need to examine the association of genetic predispositions to cognitive decline, subsequent to cardiac operations such as coronary surgeries. This current study was designed to explore the correlation between the APOE- $\epsilon$ 4 allele and cognitive dysfunction in terms of post-operative cognitive decline in patients who underwent coronary surgery after an interval of 7 weeks. The objective of this study was to analyze the effect of Apo lipoprotein E- $\epsilon$ 4 allele mediated genetic predispositions on cognitive impairment in patients with post-cardiac procedures.

## METHODOLOGY

This Cohort observational study was conducted over the patients who are undergoing coronary bypass surgery at the Cardiac Surgery Department of Ch. Pervaiz Elahi Institute of Cardiology Multan. The data was collected over a period from 1st Aug 2020 to 1st Jan 2021. The study was executed after gaining approval from the institutional review board and a written consent was also obtained from the patients undergoing coronary bypass. Additionally, the patients included in the study underwent pre-surgery neuropsychological testing in order to represent the cross-sectional view of the cognitive performance predictor in the selected patients. Patients with other serious disease conditions including cerebrovascular, psychiatric, renal or liver diseases were excluded from the selected sample of patients.

**Genotyping:** In all participants, the genotyping for the Apo lipoprotein E was performed at the post-operative stage using peripheral blood samples. The samples were stored at 4°C prior to processing. The APOE allele frequencies were determined for each patient using genomic DNA as described by Saunders et al<sup>17</sup>.

**Neuropsychological examination:** All patients included in the final sample set underwent neuropsychological examination twice, firstly at the pre-surgery phase and secondly at the post-coronary surgery phase after a duration of 7 weeks. For consistency all testing procedures were performed by the same neuropsychological examiner. However, after a careful evaluation of neuropsychological examination instruments only five instruments were selected for use in the current study as a testing battery. The study instruments comprises of Perceptual motor speed component from the Trail-Making Test part B, Short-term auditory memory (Digits Forward and Backward), Psychomotor speed, and Visual memory (Digit Symbols) were

selected from the revised Wechsler Adult Intelligence Scale. Whereas, for the short-term semantic memory the immediate and delayed components of the Randt Short Story memory test were utilized. These neuropsychological testing instruments were selected on the basis of appropriateness, relevance, reproducibility, eased administration and the availability of prior studies allowing effective comparison with already reported data sets. Therefore, the examination of pre-surgery patients was performed on the basis of perceptual motor speed, short-term auditory, psychomotor speed, visual memory and short-term memory (semantic): immediate and delayed. The scores from these instruments or tests were used for calculating individual changes over time in order to estimate the final cognitive dysfunctional ties in patients at pre- and post-coronary surgery stages.

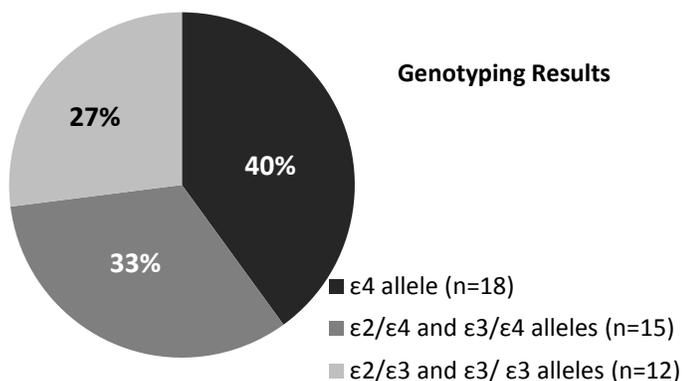
**Data Analysis:** For each patient the differences in the selected neuropsychological instruments were calculated between the pre-surgery and post-surgery at 7 weeks. Two measures including Cognitive decline (20% decrement in  $\geq$ 20% of completed tests) and Cognitive impairment index (average % decline from baseline over all test scores) were used for the assessment of cognitive performance. The multivariable logistic regression analysis was performed using SPSS using version 25. Base-line performance was represented using the scores obtained on the pre-surgery Randt Delayed test instrument. The backward elimination method was used for the selection of statistically significant features (P value <0.05). Whereas, for comparison of genotype groups, the “Fisher’s exact test” and “Wilcoxon rank-sum test” were used with categoric factors and continuous variables respectively.

## RESULTS

A total of 45 patients were studied who underwent coronary bypass surgery. The ages of the selected patients were observed in the range 44-71 years. The neuropsychological examination of the patients was performed twice, firstly at the pre-surgery phase and later at the post-coronary surgery after an interval of 7 weeks. The aim of the study is to elucidate the neuropsychological effect when the APOE genotype is present concurrently with coronary bypass surgery. Therefore, genotyping of the patients was performed that revealed the presence of the APOE  $\epsilon$ 4 allele in 73% (33) and absence in 27% (12) of the total patients respectively. Moreover, 40% of the total study samples contained a single copy of the Apo lipoprotein (E- $\epsilon$ 4 allele), 33% contained  $\epsilon$ 2/ $\epsilon$ 4 and  $\epsilon$ 3/ $\epsilon$ 4 alleles ( $\epsilon$ 4 allele present) and 27% contained  $\epsilon$ 2/ $\epsilon$ 3 and  $\epsilon$ 3/ $\epsilon$ 3 alleles ( $\epsilon$ 4 allele absent) as shown in Figure 1.

The demographic variables associated to pre-coronary surgery stage for the study sample are presented in table I. It is clearly indicated that no statistically significant difference was observed in the mean values of the descriptive variables or the baseline psychological measurement scores (means) for both the presence and absence of Apo lipoprotein E- $\epsilon$ 4 respectively. The multivariable logistic regression analysis was performed to explore the relationship between the presence of APOE- $\epsilon$ 4 allele

and cognitive dysfunction in patients who underwent coronary bypass surgery after a time interval of 7 weeks.



**Figure – 1: Apo lipoprotein E genotypes of the selected patients undergoing coronary bypass surgery (N=45).**

No significant relationship was observed with age. However, a significant relationship was observed between the presence of APOE-ε4 allele and cognitive dysfunction in patients who underwent coronary surgery after an interval of 7 weeks. Additionally, two other parameters including cognitive decline at 7 weeks and the cognitive impairment index were also used to assess the severity in cognitive dysfunction that displayed similar relationships. A strong association was observed between the presence of Apo lipoprotein E-ε4 and severity of cognitive dysfunction after performing multivariable regression analysis on the 7 week cognitive impairment index. The multivariable regression analysis results revealed model p-values of 0.0199 and 0.0289 against Cognitive deficit and Cognitive impairment index respectively. Whereas, the p values for ε4 alleles against the aforementioned measures were observed to be 0.0301 and 0.0499.

**Table – I: Demographic data and comparison between patients with (n=33) and without (n=12) the APOE-ε4 allele (N=45)**

Variables	Total Patients (n=45)	APOE-ε4 Present (n=33)	APOE-ε4 Absent (n=12)
<b>Age (years)</b>			
Median	59	60	55
Mean ± SD	58 ± 6.78	58.82 ± 6.97	55.36 ± 5.08
25 <sup>th</sup> Percentile	50.0	51	50
50 <sup>th</sup> Percentile	59.0	59.5	55
75 <sup>th</sup> Percentile	62.5	63.75	50
<b>Baseline cognitive function</b>			
Perceptual motor speed	99.01± 35.01	100.9± 34.07	97.88 ± 38.01
Short-term auditory	6.6±1.9	6.5±1.6	6.3±1.8
Psychomotor speed	35.3 ± 10.2	35.0±10.7	36.235.3±9.0
Visual retention	4.7 ± 1.8	4.9±1.8	4.2±1.6
<b>Short-term memory (semantic)</b>			
Immediate	4.9 ± 1.5	4.8±1.4	4.2±1.9
Delayed	4.4±1.6	4.3± 1.5	4.8±2.0

## DISCUSSION

In the current study we report the association of genetic predispositions with cognitive impairment in patients with post-coronary bypass surgery. Herein, we explore the relationship of the Apo lipoprotein E (ε4 allele) genotype with severity of cognitive dysfunction in 45 patients undergoing coronary surgeries. No effect of Apo lipoprotein E (ε4 allele) genotype was found on the age of patients. Moreover, the cognitive performance was not affected by the Apo lipoprotein E (ε4 allele) in patients prior to surgery, which highlights the fact that surgery procedures led to a declined cognitive functionality in genetically predisposed patients. However, a direct comparison cannot be made with other studies due to the availability of a limited number of studies that clearly describe the current status of APOE ε4 and its role in post-surgery cognitive decline. Additionally, a number of studies are reported but with different study designs, population samples follow up lengths and a wide range of cognitive measures<sup>6,8,17,18</sup>.

Most evidently, variable trends of APOE ε4 association with cognitive impairment after surgery have been reported in literature. Some studies show no association of APOE ε4 with cognitive deficit after an interval of one to eight years post-cardiac and non-cardiac surgeries<sup>5,19-22</sup>. Contrary to that Bartels et al. have reported a lower cognitive improvement over a period of five years post-cardiac surgery among patients with APOE ε4 allele genotype<sup>23</sup>. Moreover, the association of APOE ε4 with cognitive decline was not addressed for the group of patients with non-cardiac surgery<sup>24,25</sup>.

Additionally, Bown et al have demonstrated that the presence of APOE-ε4 genotype considerably leads to lower cardiac output and neuropsychological performance<sup>6</sup>. This also points towards the fact that the presence of APOE-ε4 displays important implications for associations between brain and cardiac health specially in older individuals<sup>26</sup>. Similarly, the APOE ε4 based outcomes of our study depict the association of APOE-ε4 allele and cognitive dysfunction in patients who underwent coronary bypass surgery. Our results are particularly in line with the findings of Tardiff et al who investigated the genetic basis for cognitive decline after coronary bypass in a set of 65 patients<sup>4</sup>. Towards this, a less stringent PCOD definition was used and a significant association was observed between the ε4 allele and decline in short-term memory 6 weeks after surgery<sup>27</sup>. Later on Tardiffs study was replicated by Steed et al using a set of 111 patients. Observably no significant association was identified between the ε4 allele and cognitive decline after cardiac surgery<sup>28</sup>.

Interestingly, previously different predictors have been implicated to be important for cognitive decline. Some of the most important descriptors are age and education level. Age is identified as important predictor for cognitive outcomes but different trends have been observed over the reported literature<sup>24</sup>. In the current study no statistically significant relationship was observed with age. This observation of age as a non-predictor of cognitive outcome is reported in a number of studies but this can be attributed to the use of smaller sample sizes<sup>25</sup>. Contrary to this a number of other studies have reported

a substantial association of APOE  $\epsilon$ 4 and cognitive function with age. Thus, it is shown that APOE  $\epsilon$ 4 carrier patients above 70 years of age display considerable association between APOE  $\epsilon$ 4 and cognitive functionality in comparison to younger patients<sup>5</sup>. Additionally, it is also important to consider the significance of the preoperative cognitive examination as it forms a crucial component for the appropriate examination of postoperative trajectory of cognitive functionality<sup>26,27</sup>. Therefore, in the current study neuropsychological testing was performed for the pre-coronary surgery stage which was followed by the post-surgery neuropsychological examination at an interval of 7 weeks. The inclusion of this aspect in the present study adds value to the current study design. Particularly, from our study it can be concluded that the multivariable logistic regression analysis was performed for the factors including APOE  $\epsilon$ 4, age and preoperative score. Here, a considerable association was observed between the APOE  $\epsilon$ 4 and cognitive impairment based on the measures of neuropsychological testing at 7 weeks post-coronary surgery. Therefore, it is proposed that the APOE  $\epsilon$ 4 genotype displays an observable association with cognitive deficit post-coronary surgery. Moreover, the patients undergoing cardiac surgeries may be more prone to worsening of cognitive functionality due to physiologic stress.

### CONCLUSION

A significant relationship was observed between the presence of APOE- $\epsilon$ 4 allele and cognitive dysfunction in patients who underwent coronary bypass surgery after an interval of 7 weeks. Moreover, no statistically significant relationship was observed with age.

### AUTHOR'S CONTRIBUTION

**Hussain S:** Conceived idea, Designed methodology, Data analysis, Manuscript writing, Final critical review of manuscript

**Malik RA:** Data analysis, Manuscript writing, Literature review

**Khan MY:** Manuscript writing, Data analysis, Data collection, Literature review

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